UNIVERSIDAD AUTÓNOMA DE MADRID

FACULTAD DE MEDICINA

DEPARTAMENTO DE PEDIATRÍA

Electrocardiographic characteristics of children with seizures and syncope

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

(Ph.D.)

IN MEDICINE AND SURGERY

Daiana Cassater

Madrid, 2017

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Profesor Federico Gutiérrez - Larraya Aguado, Professor Profesor Asociado de la Universidad Autónoma de Madrid, Departamento de Pediatría

HACE CONSTAR:

que la presente memoria de Tesis Doctoral presentada por Daiana Cassater y titulada "Electrocardiographic characteristics of children with seizures and syncope" ha sido realizada bajo su dirección en el Servicio de Cardiología Infantil, Departamento de Pediatría, Hospital Universitario La Paz, Madrid.

El trabajo recogido en dicha memoria se corresponde con el planteado en el proyecto de tesis doctoral aprobado en su día por el órgano responsable del programa de Doctorado.

Y para que conste, en cumplimiento de la legislación vigente, informo favorablemente sobre la referida Tesis Doctoral y autorizo su presentación para su admisión a trámite.

El Director de la Tesis

Fdo.: Federico Gutiérrez - Larraya Aguado

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Alla mia mamma, che mi è sempre stata vicina: i miei successi sono i tuoi

Ai miei errori, che mi hanno insegnato a camminare da sola

Ai miei pazienti di ieri e di domani, per avermi insegnato l'umiltà di imparare e di migliorare sempre.

Gracias a la Dra Marta Ortega Molina por su trabajo y a los médicos de la Unidad de Urgencias Pediátricas H. La Paz, Madrid.

"Don't let the noise of others' opinions drown out your own inner voice. And most important, have the courage to follow your heart and intuition. They somehow already know what you truly want to become. Everything else is secondary". (S.J.)

ABSTRACT

This dissertation is an observational, cross-sectional study describing the ECG findings of a pediatric population attended to in an Emergency Department for febrile seizures, nonfebrile seizures or syncope.

The idea of the study originated from the casual observation that the ECGs of children that had experienced a seizure were unexpectedly abnormal although no data on the subject had ever been systematically provided in the medical literature.

This marks an important - and in my opinion unjustified - difference between the pediatric and the adult population, in which the realization of an ECG after an episode of loss of consciousness is far more frequent.

From just a merely practical standpoint, the ECG is an important, powerful and cheap diagnostic tool and its use is at almost any clinician’s reach; when examining the theoretical basis of the problem, a few more considerations are worth making.

First of all, the cardiovascular and the nervous systems share some molecular structures, the ion channels, that, when mutated, become responsible for the so-called channelopathies. These conditions include some forms of epilepsy as well as arrhythmogenic diseases. The tissue - specificity of the mutated forms of the channels is not absolute and channelopathies may have both a neurological and a cardiac

expression, as a variety of reports have been pointing out.

Secondly, the mutations that originate channelopathies are present since birth, despite, in many cases, diagnosis is made during adulthood. Even though a variety of explications has been provided to this point, including the effects of hormones on the ion channels themselves, it is worth mentioning that the localization and functioning of the ion channels within the cells (such as the myocytes) varies throughout childhood.

On the other hand, channelopathies may lead to structural changes: just as an example, epicardial and interstitial fibrosis has been demonstrated in the hearts of patients with Brugada syndrome.

These considerations make channelopathies a group of conditions to be potentially regarded as “evolutive diseases”, so that the ECG tracings of certain children should be probably studied from this perspective as well. Undoubtedly, future research on particular populations of children, like those that we tried to identify in our study, should be carried out.

In our work, the majority of patients presented at least minor electrocardiographic alterations, being the most common those of the repolarization phase. This is an overall heterogenous group of findings, which includes the prolongation of the QT interval, the excessive widening of the QRS/T wave angle, the deviation of the ST segment,

the increase of the QT dispersion and the so-called "early depolarization pattern". In our study, each one of these ECG finding seems to take on a different meaning according to the clinical picture (seizure vs. syncope, fever vs. no fever) and its persistence beyond the acute episode.

A second group of ECG abnormalities involves the depolarization phase. Of particular interest is the fragmentation of the QRS complex, something that has been extensively studied in the adult population and practically ignored among children - its prevalence in our population has been as high as 44%, especially among febrile children.

In conclusion, this study highlights that children attended to for febrile, nonfebrile seizures and syncope are an unexpectedly heterogeneous group from an electrocardiographic point of view, with an equally unexpectedly high prevalence of abnormal ECG findings.
These observations might help clinicians further clarify the natural history of channelopathies, stratify the prognosis of certain conditions (like nonfebrile seizures in which early repolarization is found), create a clearer pathophysiological link between the cardiovascular and nervous system, which are already known to share some molecular structures, and lay the foundation for further prospective clinical studies exploring the changes of the pediatric ECG into adulthood in selected populations of children.

RESUMEN

El presente trabajo de investigación es un estudio observacional transversal que describe los hallazgos electrocardiográficos de una población pediátrica atendida en Urgencias por convulsiones febriles, convulsiones afebriles y por síncope.

La idea del estudio originó de la observación casual que los electrocardiogramas de los niños que acababan de presentar una convulsión febril eran inesperadamente anormales. No obstante, no había ningún dato al respecto en literatura.

Este punto representa una diferencia importante - y en mi opinión injustificada - entre la población pediátrica y adulta, ya que en esta última se suele realizar un ECG después de un episodio de pérdida de conocimiento con frecuencia mucho mayor.

Desde un punto de vista meramente práctico, cabe destacar que el electrocardiograma es una herramienta diagnóstica importante, potente y barata, al alcance prácticamente de cualquier clínico; por otro lado, cuando examinemos las bases teóricas del problemas, merece la pena añadir alguna consideración más.

Primero, el sistema cardiovascular y nervioso comparten unas estructuras moleculares, los canales iónicos, que, en el caso sean afectados por unas mutaciones, ocasionan las llamadas “canalopatías”. Estas condiciones incluyen algunas formas de epilepsia y de

enfermedades arritmogénicas. La especificidad tissular de las formas mutadas de los canales iónicos no es absoluta, y las canalopatías pueden tener tanto una expresión clínica neurológica como cardiovascular, como se informa en algunos artículos más recientes.

En segundo lugar, las mutaciones responsables de las canalopatías acompañan al individuo desde su nacimiento, si bien el diagnostico suele realizarse durante la edad adulta. A pesar de que una gran variedad de explicaciones haya sido ofrecida al respecto, incluido el efecto sobre los mismos canales iónicos que las hormonas sexuales tendrían, cabe destacar que tanto la localización como el funcionamiento de los propios canales dentro de la célula (como el proprio miocito) varían a lo largo de la infancia.

Por otro lado, se ha demostrado que las canalopatías pueden conllevar cambios estructurales. Por ejemplo, en los corazones de los pacientes con síndrome de Brugada, se ha demostrado la presencia de fibrosis epicárdica e intersticial.

Todas estas consideraciones hacen que haya que considerar las canalopatías como “enfermedades potencialmente evolutivas”; por ello, los ECG de algunos niños, probablemente, deberían de valorarse bajo este punto de vista. En el futuro, por lo tanto, la investigación clínica deberá dirigirse a la valoración especifica de ciertas poblaciones de niños, como aquellas que hemos tratado de identificar en nuestro estudio.

La mayoría de los electrocardiogramas que hemos examinado en nuestro proyecto de investigación presentaba al menos unas alteraciones menores, siendo las más frecuentes aquellas de la fase de repolarización.

Éste es en conjunto un grupo heterogéneo de hallazgos electrocardiográficos, que incluye la prolongación del intervalo QT, el ensanchamiento excesivo del ángulo entre el eje del complejo QRS y el eje de la onda T, la desviación del segmento ST, el incremento de la dispersión del QT y el llamado "patrón de repolarización precoz". En nuestro estudio, cada uno de estos datos electrocardiográficos asume un significado diferente en relación al contexto clínico (convulsión vs. síncope, fiebre vs. ausencia de fiebre) y su persistencia tras el acontecimiento agudo.

Un segundo grupo de alteraciones electrocardiográficas involucra la fase de despolarización. De interés particular es la fragmentación del complejo QRS, algo que ha sido extensivamente estudiado en la población adulta y prácticamente ignorado en los niños - su prevalencia en nuestra población se sitúa en un alto 44%, siendo más elevada entre los niños con fiebre.

En conclusión, este estudio evidencia que los niños atendidos por convulsiones tanto febriles como afebriles, y por síncopes, representan un grupo inesperadamente heterogéneo desde el punto de vista

electrocardiográfico, con una prevalencia de alteraciones electrocardiográficas también inesperadamente elevada.

Nuestras observaciones podrían ayudar a los clínicos a aclarar la historia natural de las canalopatías, estratificar el pronostico de algunas condiciones (como las convulsiones no febriles en las que se detecte un patrón de repolarización precoz), crear un mecanismo fisiopatológico más claro entre los sistemas cardiovascular y nervioso - que comparten estructuras moleculares clave como ciertos canales iónicos - y sentar las bases de futuros estudios clínicos que exploren los cambios del ECG pediátrico hacía la edad adulta en poblaciones seleccionas de niños.

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PART 1.

Chapter 1.

Introduction

Foreword

One morning as many others, I happened to see the ECG tracing of an two-year old boy admitted to the pediatric ward after a febrile seizure.
It showed markedly abnormal repolarization phase, without a diagnostic pattern per se, that reverted in a following ECG.
I tried to give an explanation for that tracing, but, to my disappointment, I discovered that there had been no study describing the characteristics of the ECG tracings of children attended to for a recent seizure.

That day was the "moral beginning" of this study.

A. Generalities and key concepts

Seizures are a very common clinical problem during childhood.

Up to 4% of individuals are expected to present a seizure throughout infancy and in our setting, seizures represent up to 2% of the Emergency Department (ED) visits over one year [1].

While being so common, their pathophysiology is far far being completely clear in most of the cases that come to medical attention. The term "convulsion" is often and incorrectly used in the clinical setting as a synonym for seizure, but convulsions actually represent only a variety of seizures and the term is just descriptive of what is seen to happen to the patient [2].

There is a large amount of literature on the management of the first episode of seizure in children and adults [2,3,4] in which seizures are simply defined as the clinical expression of either an acute primary disruption of the normal organized electrical activity, or the possible symptom of a structural damage of the brain due to a toxic, metabolic, infectious or traumatic agent.

However, seizures can also be the clinical expression of a similar distortion of the electrical activity of the heart, representing indeed the clinical expression of a cardiac arrhythmia [3,4,5]. On a practical level, this poses an additional difficulty to the clinician dealing with the

differential diagnostic process of a seizure, but it also triggers some further questions: which is the real prevalence of cardiac arrhythmic diseases in children presenting with a seizure? Is there a relationship between recurrent seizures (or epileptic syndromes) and arrhythmogenic diseases?

The key to answer the latter question is the concept of "channelopathy", which has recently been introduced in medical literature [6,7], referring to the fact that those ion channels responsible for the sequential transmembrane passage of calcium, potassium and sodium currents across the electrically active membranes of neuronal, cardiac and muscular tissues, when affected by genetic mutations altering their molecular structure, become responsible for a wide range of conditions, from Brugada syndrome to Dravet syndrome - to name but a few.

However, being the tissue-specificity of such channels not absolute, a mutated ion channel may actually be found in various tissues in the same individual, conditioning therefore - at least on a theoretical level - the co-existence of dysfunctional channels in two or more tissues in the same patient. As a support to this hypothesis, in the last years, various Authors have provided case reports of patients in whom the co-existence of epileptic syndromes and arrhythmic syndromes has been demonstrated [5,8].

The concept of channelopathy offers a new way of approaching patients. Discarding cardiac pathology in patients diagnosed with neurologic diseases has become clinically relevant.

Another important point is the relationship between electrical and structural disease in the affected organs, since ionic channels do possess structural functions as well.

Although this concept is still a matter of debate and intense study, it might explain on the one hand the progressive nature of the clinical course of certain diseases (for instance, the Dravet syndrome) and on the other hand, it might as well offer one possible, valid explanation as to why some channelopathies are rarely diagnosed during childhood (for instance, Brugada syndrome), even though the mutated gene is present since birth.

We are going to examine in detail each of these points in the following paragraphs.

B. Seizures in childhood: clinical approach and differential diagnosis

Seizure is to be defined as a sudden surge of a synchronous and abnormal electrical activity in the brain. This can be generalized or focal

depending on the extension of the brain area where the phenomenon takes place. On a clinical level, a seizure can therefore express itself with motor, sensitive or psychical symptoms and signs, implying that what it is generally referred to as a “convulsion” and comes to medical attention is neither always a seizure, and if it is a seizure, it might not be the first seizure experienced by the patient.

That said, the majority of children taken to the Emergency Department and diagnosed with a true “seizure” actually present a convulsion, i.e. a seizure resulting in motor symptoms. History taking allows to better define the seizure, and to further classify it as a generalized seizure since its onset or rather as a secondarily generalized seizure, being it focal (or “partial”) at its beginning. This distinction is important because it points out the presence of an epileptogenic focus in the brain from which the abnormal electrical activity would originate.

Some children present with a particular form of seizure which would be defined as generalized, even though they do not express themselves as convulsions: absences. These are best clinically described as moments of lack of response of the patient, that may interrupt or not his or her activity, leaving him or her staring in the void, with no posterior memory of the episode. Hyperventilation generally evokes the spell.

Childhood is the typical age of onset of absences, especially between age four and eight years.

To sum up, seizures may be either partial or generalized, depending on the extension of the brain tissue involved in the surge of the abnormal electrical activity. Partial seizures may become secondarily generalized and may or not affect consciousness, in which case they will be defined complex seizures (Figure 1).

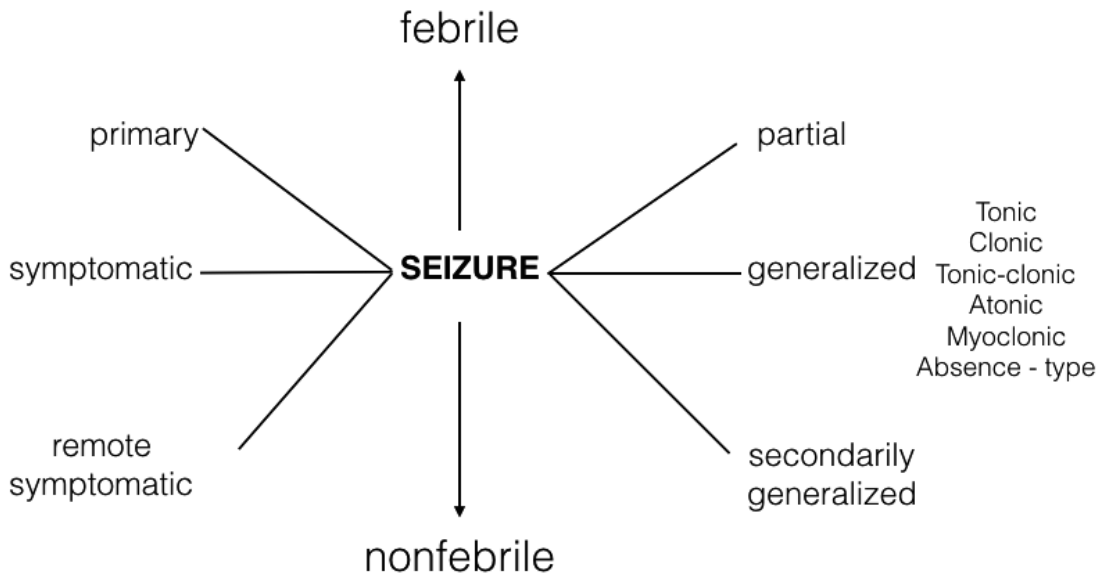


Figure 1. Classification of seizures. See text for details. Image of the Author's own design.

Generalized seizures can be described according to the clinical picture they give rise to as tonic, clonic, tonic-clonic, myoclonic, atonic and absence-type seizures.

When a patient comes to the Emergency Department either with a possible ongoing seizure or with a history of seizure, the first step is stabilizing him or her following the classical ABC algorithm and rapidly carrying out a basic neurological examination. Both history and investigations should be aimed at discarding that the seizure is the symptom of a systemic or of a neurologic structural, toxic, infectious disease [9]. In a very recent work on the epidemiology of seizures in children presenting at a third-level hospital in Northern Italy, Bergamo and coworkers [10] found out that 19% of all the patients attended to for a seizure actually presented for a remote symptomatic seizure, i.e. a seizure occurring longer than 1 week following a disorder that is known to increase the risk of having a seizure.

Interestingly enough, although the majority of Authors mention cardiac arrhythmias as a possible underlying cause of convulsions, and therefore as a differential diagnosis of seizures, the Author of this research has never found the ECG to be mentioned as an investigation to be carried out in those pediatric patients presenting with a suspected seizure [11, 12] (Table 1).

SEIZURE WORK-UP (adult)	SEIZURE WORK-UP (child)
History, physical examination in all patients	History, physical examination in all patients, febrile and nonfebrile.
* **Lab tests,** including electrolyte panel, glucose, pregnancy test in women of childbearing age * **Neuroimaging** especially in first time seizures * **ECG:** obtain in every patient * **Lumbar puncture** if clinical suspicion of meningitis, encefalitis and/or inmunosuppression	* **Lab tests, chest X-ray, urine test**: based on clinical examination in febrile seizures, if indicated. * **Lumbar puncture**: not indicated in well-appearing, fully immunized children and NO signs of meningitis/encephalitis. Lower threshold if pre-treated with antibiotics or not fully immunized. It should be considered in children with nonfebrile seizures too young or developmentally delayed to evaluate mental status. * **Electrolyte panel**: not recommended. * **Neuroimaging:** consider in case of focal, prolonged febrile seizures o persistent altered mental status, abnormal examination, signs of increased intracranial pressure, suspicion of trauma or postictal deficit that does not resolve quickly. * **Electroencephalography**: not recommended in the ER.
Toxicology screening: in every patient depending on guidelines	**Toxicology screening**: according to suspicion

Table 1. Differences in the recommendations for the management of adult and pediatric patients attended to for seizures in the Emergency Department. Note that the need for obtaining an ECG is mentioned only in the case of adults. See References in text. Table of the Author's own design.

A variety of conditions can mimic a seizure. The most common one is syncope, although what the two entities really share - at least in the case of generalized and complex seizures - is the loss of consciousness.

Syncope may lead to brief tonic clonic movements due to short generalized brain hypoxemia but they do not dominate the clinical picture. It is usually commented that the full return to an alert and functional state is more rapid in the case of syncopal events rather than in the case of seizures, which tend to leave the patients dizzy and sleepy for hours after the critical event.
Clinicians should never forget that arrhythmias leading to brain hypoxemia may present as generalized seizures. In this regard, a seizure per se does not discard an underlying cardiac issue.

B1. Febrile seizures

A particular subgroup of seizures in children is that of febrile seizures.
By definition, febrile seizures may only affect children between 6 and 60 months of age, with no prior history of nonfebrile seizures, and with no coincident neurological infection or structural neurological disease.

The diagnosis of febrile seizure is a clinical one and the attention of clinicians has long been concentrated on the problem of distinguish

those children in whom seizures and fever may be the clinical expression of an infection of the central nervous system and in whom therefore the realization of a lumbar puncture and the rapid start of a systemic antibiotic treatment is mandatory from those children in whom fever proceeds from a different source.

With the spread of vaccinations against *Hemophilus Influenzae B* first and *Pneumococcus spp*. then, this problem, while still remaining in our setting, has been progressively downsized, and attention has been focused on answering the following question: why do certain children present seizures when having a fever and others do not?

There is probably not just one answer to this question. In some cases it may be a coincidence of multiple factors, such as a favoring environment recreated by pro-inflammatory cytokines that typically accompanies the rising of body temperature.

In 2005 Dubé and coworkers [13] demonstrated that, first of all, IL-1 beta receptor–deficient mice were resistant to experimental febrile seizures, and, secondly, that high IL-1 beta doses induced seizures in IL-1 beta receptor–expressing mice, proving that IL-1 beta signaling pathway plays a critical role in the genesis of febrile seizures, although it may be not the only one.

The fact that certain individuals are more prone to have seizures with the rising of temperature than others and that there is a certain recurrence within families seems to suggest the existence of a genetic factor as well.

A genetic model is indeed offered by the GEFS+ syndrome. This condition is characterized by febrile seizures that persist beyond age 6 years and recur in the members of a given family. Several genetic variants have been described, their commonality being the fact that the affected individuals carry a mutated variant of the alpha subunit of the voltage-dependent sodium channel regulating the depolarization of the neuronal membrane. Such mutation would increase the individual's temperature sensitivity explaining his or her tendency to suffer from an increased rate of seizures whenever his of her body temperature raises.

It seems logic to extrapolate the model to those cases of febrile seizures which do not meet the criteria of GEFS+ but only with the purpose to admit that there may be a part of the general population in whom febrile seizures can actually represent a clinical phenomenon alerting to their particular genetic tendency to respond to the variations of their inner temperature.

It may or may not reflect the presence of a disease, or - better said - of a genetically mutated ion channel - at neurological or cardiac level.

Only if the phenomenon of febrile seizures is systematically studied, conclusions will be possibly drawn.

C. Ion channels and "channelopathies": introducing old and new concepts

C1. The sodium channel structure and its mutations. Temperature sensitivity.

There are various type of ion channels, depending on the ion implicated in the transport across the cellular membrane.
Ion channels are further classified according to the trigger regulating their opening, which can be a molecule (ligand-gated channels), a variation of the transmembrane voltage (voltage-gated channels) or a change in structural conformation (mechano-sensitive channels).

The voltage-gated sodium channel is named so because it is implicated in the transportation of the sodium ions into the membrane in response to changes in the membrane potential. It consists of a primary alfa and of several secondary beta subunits.

The beta subunits are smaller than the alfa subunit and their role seems to be that of modulating channel gating and regulating the arrival of the channel itself to the membrane.

The alfa subunit consists of 4 homologous domains forming a pore, each domain consisting in turn of six segments (named S1 - S2 - S3 - S4 - S5 - S6) crossing the membrane and joined by alternating intra- and extracellular loops [7]. Each S4 segment has a positively - charged amino acid at every third or fourth position. These amino acids serve as the sensor of the transmembrane voltage, as the movement of these charges across the membrane during channel gating generates small currents, conditioning in turn a change of the conformation of the S5 segment, which would be the critical element of the channel gating process.

To open once more, the channel must pass through a phase called "inactivation", which is fundamental in preventing premature re-excitation. This is a process is important for various reasons.

First of all, rapid inactivation of the channel occurring immediately after its activation is responsible for the fact that the electrical activity within a given tissue may proceed in an unidirectional manner. In this way, electrical conduction becomes possible.

Secondly, the repetitive activity of channels gives birth to a slower inactivation process, a sort of "use-dependent inactivation", that would help prevent ventricular arrhythmias when a rapid sequence of depolarizations occurs. In both cases, a change in the conformation of the sodium channel occurs, with the occlusion of the pore taking place. Interestingly, the sequence of amino acids between the third (DIII) and the fourth (DIV) domain of the alpha subunit is highly preserved through species and sodium channels subtypes, pointing to its high importance in the process (Figure 2).

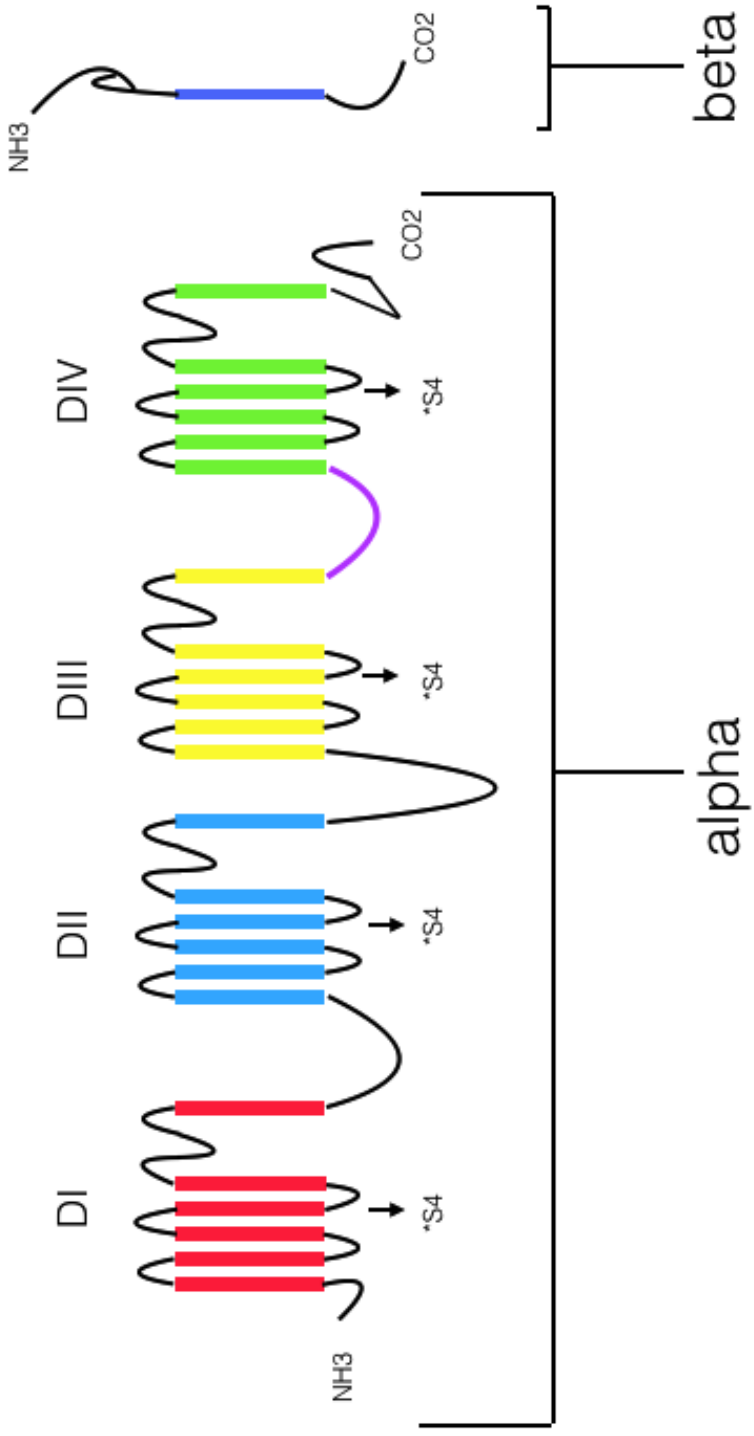


Figure 2. Schematic representation of a sodium channel. The alpha subunit is made up of four domains, each of them containing six transmembrane subunits, the fourth one acting as voltage sensor. The sequence between DIII and DIV is highly preserved among species. Freely modified from Egri et al. Reference in text.

Sodium channels possess an intrinsic sensitivity to temperature. The rates of activation, deactivation and slow and rapid inactivation of the channel increase with the increase of temperature. This is mathematically expressed by the "Q_{10}" coefficient, which is the mathematical representation of the degree to which a biological process depends on temperature. It is defined as the ratio between the rate of a biological process at a given temperature and the rate at which it takes place at that same temperature plus 10°C. In the case of voltage-gated sodium channels, Q_{10} ranges between 2–4 for Na_Vs, which indicates that an increase in temperature increases gating kinetics as well.

Biologically, it has been demonstrated that variations in body temperature may condition sodium-channels regulated activities, like the start of neuronal activation and cardiac depolarization.

As far as humans are concerned, an interesting work was published in 2006 in which Keller et al. [14] described a novel mutation of the SCNA5A gene causing a shift of the steady-state activation threshold at higher temperatures, indicating that in mutation carriers a febrile process would be able to reduce sodium current amplitude and trigger therefore ventricular fibrillation, as a clinical manifestation of Brugada syndrome. The researchers reproduced the electrophysiological system in vitro, trans-infecting a cell line with the mutated gene. The mutation had been identified in a male patient with clinically symptomatic

Brugada syndrome and consisted in the change from phenylanine to serine at residue number 1344 (F1344S), located in the fifth segment (S5) of the third domain (DIII) of the alpha subunit. In vitro, the rising of the environmental temperature from 22 to 40.5°C increased the rate of activation for both wild type (WT) channels and F1344S mutant channels, but what was even more important, an 8 mV-shift increase in the activation potential of the mutated channels was also demonstrated at a 40.5°C-temperature compared to the WT channels, which translated into a net loss of function of the sodium channels, as it reduced the availability of total sodium current.

This work is interesting because it offers both a clinical, in-vivo, and vitro demonstration of the implications of temperature-sensitivity of the cardiac voltage-gated sodium channels. In this work the Authors demonstrate that temperature sensitivity express itself as a loss of function in that it shifts the G/V curve upwards, i.e. it is necessary to have a more positive transmembrane voltage for the sodium channel to be activated. The net result of a rising in the environmental temperature is a functional inactivation of the sodium channels, a net loss of the total transmembrane sodium positive inward activating current, and therefore, a propensity to develop arrhythmias.

However, other researchers have found out alternative pathways to get to the same point, i.e. a functional loss of total sodium current. For instance, in 2009 Samani and coworkers [15] published another paper in which they studied a missense mutation of the SCNA5 gene, previously identified in a family affected by the Brugada syndrome. The effects of the mutation, V1340I, were studied at 22°C, 32°C, 37°C and 40°C, reporting the effect of the rising temperature on the sodium currents both through the wild type (WT) channels and the mutated channels.
They found out that at 22°C, mutated channels generated markedly diminished sodium currents compared to the WT channels. They also found out that V1340I-delQ significantly attenuated the peak current density compared to the WT-delQ at 32°C, 37°C and 40°C.
In addition, the mutation accelerated the recovery time course from fast inactivation compared to the WT channels at 40°C.

There are probably several electrophysiological molecular mechanisms implicated in the temperature sensitivity displayed by sodium channels in patients affected by Brugada syndrome. The key concept is that sensitivity to temperature variations is a clinical fact and it is supported by in vitro demonstrations, although the explanations may be multiple and therefore, a unifying mechanism explaining the pathophysiology of the disease on a molecular level is still lacking.

Temperature sensitivity is an important characteristic of sodium channels expressed in the neuronal tissue as well.

As previously stated in the paragraph introducing the theme of febrile seizures, some patients do have a particular sensitivity to the rising of body temperature that expresses itself in the form of febrile seizures, something that clinicians tend to consider frequent and benign, and that, in most cases, is so.

What are the neurological pathologies which serve as a paradigm of the mutations of the voltage-gated sodium channels in the CNS thus demonstrating the concept of temperature sensitivity in this setting?

GEFS+ (Generalized Epilepsy with Febrile Seizures Plus Syndrome) and Dravet syndrome are both due to a mutation in a voltage-sodium channel. Several mutations have been identified, mainly involving the SCN1B isoform in the case of the GEFS+ and the SCN1A isoform in the case of the Dravet syndrome respectively, but mutations involving the SCN2 gene have been described as well.

Dravet syndrome and GEFS+ are actually interesting examples of how a mutation of the same gene may give birth to very different clinical entities, GEFS+ having a benign prognosis and Dravet syndrome being characterized by a particularly poor outcome. In both cases, affected individuals are prone to recurrent febrile seizures. Again, the molecular mechanism are heterogenous.

In a study of 2010, Wimmer and coworkers [16] examined a mouse model that was heterozygous for the beta1 C121W mutation that had been previously demonstrated to be related to the human phenotype of GEFS+ syndrome. Increasing the temperature of the animals, the researchers obtained an epileptiform activity both at a clinical and at an EEG level. On a molecular level, the Authors observed that the mutant mice did not show the beta1 protein in the axon initial segments (AIS) region as the wild-type (WT) counterparts did, suggesting that a part of the pathology observed depended on a disruption of the topography of the proteins expressed on the membrane of this very important part of the neuronal cell, where the action potential originates. The beta subunits are not actually necessary for the alpha subunits to be localized on the axon initial segments region: the alpha units could still be located there; however, the neurons carrying the mutations resulted to be more excitable in two ways.

First, when providing current injections, CW cells displayed bursts of longer duration as compared to WT cells with a concomitant increase in the number of action potentials per burst. This means that CW cells were able to give rise to action potentials more frequently, i.e. they showed an intrinsic hyperexcitability; secondly and perhaps more importantly, the Authors found out that an increase in temperature increased in turn axonal excitability in both WT and CW neurons;

however, this increase was significantly larger in CW cells, indicating that the CW mutation rendered the axon initial segments more temperature-sensitive. This increase in neuronal excitability at higher temperatures may be the explanation for the tendency to develop febrile seizures that both the mice in the experimental model and the patients have.

To sum up, this study offered a model explaining the temperature sensitivity of the sodium channel in neuronal cells and the implications of one of its mutated versions causing the GEFS+ syndrome. Interestingly enough, the Authors underline an important point, on which we will later return: the relationship between the mutated protein and the extracellular matrix, which would imply a connection between the electrophysiological and the structural consequences of the mutations.

Summarizing the evidence on voltage-gated sodium channels, what we know at present is that they are widely expressed in tissues capable of electrical activity, and that they consist of one alpha subunit, which is the one truly implicated in the gating process and in granting the passage of the ions, and of some beta subunits, which play a regulatory role. Sodium channels are intrinsically temperature-sensitive, a property that express itself on a clinical level; mutations of the isoforms of this

channels are implicated in the pathogenesis of diseases such as GEFS+, Dravet syndrome and Brugada syndrome in which the rising of body temperature plays a critical role in generating an abnormal electrical activity of the cardiac or neuronal tissue.

These conditions serve as a paradigm of the sodium channelopathies (Table 2).

Keller et al. (2006)	They studied an in vitro and in-vivo demonstrated mutation (F1344S), located in the S5 of the DIII of the alpha subunit of the NaV1.5 channel. At 40.5°C they observed both an increased rate of activation of the channels and an upward shift of the G/V curve (a more positive voltage to activate the channel), which practically translated into a net loss of function of the sodium channels and a reduction of the inward sodium current.
Samani et al. (2009)	They studied the mutation V1340I of SCN5A: the mutated channel generated a significantly attenuated peak current density compared to the wild- type (WT) channel at 32°C, 37°C and 40°C. The mutation accelerated the recovery time course from fast inactivation compared to the WT channels at 40°C, overall reducing the net sodium current.
Wimmer et al. (2010)	They studied a mice model carrying a mutation (C121W) related to the human phenotype of GEFS+. Beta subunits were not correctly located on the axon initial segments region and the neuronal cells could originate more frequent and longer bursts with increasing temperatures.

Table 2. Summary of the main studies demonstrating Brugada syndrome and GEFS+ as paradigm of channelopathies. Table of the Author's own design.

C2. Potassium channels. Molecular structure and mutations.

Human potassium channels are divided into calcium-activated, inwardly-rectifying, tandem-pore domain (channels regulated by a variety of mechanisms such as variations oh pH, O2, mechanical stretch… and which are named so because possess two alfa subunits forming dimers), and voltage-gated channels, important in determining the so-called Ito1 (inactivating transient outward current), IKur, IKr, IKs - the ultrarapid, the rapid and slow component of the delayed rectifying current (Table 3).

Let us examine some of these in detail.

Calcium-activated	An alpha subunit which is a tetramer forming the pore permeable to K ions and including a voltage and a calcium sensor, plus a beta subunit	Implicated, for exemple, in the regulation of vascular tone
Inwardly-rectifying	The basic block is made of two subunits that contain two segments linked by a P-loop; 4 of such subunits may aggregate to form either homo - or heterotetramers.	KCNJ2 mutation is responsible for Andersen's syndrome (involving both CNS and the heart)
Tandem - pore domain	Two alpha subunits forming a dimer and regulated by a variety of mechanisms (variations of the cellular pH, mechanic stress...)	
Voltage - gated	A tetramer of alpha subunits, each with six transmembrane segments, and multiple regulatory beta subunits. Alpha subunits include the families of KvNx, HERG, KvLQT1	Generate the main K currents, like: * Ito1 * IKur, IKr, IKs

Table 3. Potassium channels classified according to their molecular structure. See text for details. Table of the Author's own design.

In the heart, potassium channels are differently expressed throughout the myocardium [17].

Voltage-gated channels consist of alpha subunits and multiple beta subunits, with a regulatory role. The alpha subunits include the subtypes KvNx, HERG and KvLQT1. For a complete potassium channel to be constituted, a tetramer of alpha subunits must be assembled, each of them being composed of six segments. Members of the KvNx subfamily co-assemble to form hetero-multimers while members of the HERG and KvLQT1 subfamilies assemble as homotetramers. The voltage-gating mechanism is very similar to that of the voltage-gated sodium channels, with the S4 segment carrying a positively-charged amino acid at approximately every third position. Depolarization of the membrane determines an outward movement of the S4 segment, and some further conformational changes that render the channel selectively permeable to potassium ions.

Inwardly-rectifying potassium channels have a much less complex structure. They consist indeed of only two subunits that contain two segments linked by a P-loop. These channels give rise to a variety of rectifying currents. Their role is to revert the transmembrane voltage, but at a time and with a rhythm that varies within the cardiac muscle.

What are the main potassium currents in the heart cell?

There are are two components of the transient outward current: I_{to1} and I_{to2}, which is a calcium-activated chloride current.

I_{to1} is a K-outward current in turn composed of a fast and a slow component ($I_{to'f}$ and I_{tos}).

The fast component is especially found in the human atrium; both the fast and the slow components may be found in the ventricle. Those myocardial regions that possess the relatively shortest action potentials - such as the epicardium, right ventricle, and the septum - have higher levels of I_{to} expression.

Cardiac cells typically have at least one transient outward current and different delayed rectifiers to manage the overall duration of the action potential. Transient outward current is generated at the very beginning of the action potential itself, whereas delayed rectifier K currents (I_{Kur}, I_{Kr}, and I_{Ks}) typically control the third phase of the action potential, thus directly determining its duration in the cell type where they are located, since their deactivation is sufficiently slow to allow potassium to flow out of the cell, thus re-polarizing it. The difference in the density of these channels is indeed what determines the difference in the duration of the action potential throughout the myocardium.

I_{Kur} is highly expressed in atrial myocytes and is a basis for the much shorter duration of the action potential in the atrium.

I_{Kr} are especially found in the left atrium and ventricular endocardium. I_{Ks} is less expressed in mid-myocardial myocytes, the cells that actually have the longest action potential duration across the myocardial wall. Phases 0, 1 and 2 of the action potential are dominated by the I_{K1} inward rectifier current, which sets the negative resting potential in both atrial and ventricular cells.

Another type of potassium channel is the acetylcholine-activated K channel, a member of the G protein–coupled inwardly rectifying potassium channels. This channel is highly expressed in the SA and AV nodes and in the atria. The binding of acetylcholine to the muscarinic receptor activates the protein Gi coupled to the K channel, thus activating it.

To sum up, potassium channels in the heart are basically implicated in the regulation of the transmembrane potential, setting the basal negative potential in the resting cell (phase 4 of the action potential), opposing to the upstroke of the potential itself after the phase 0 determined by the inward sodium current by means of the transient outward potassium currents and regulating the overall duration of the action potential (phase 3) through the delayed rectifier currents. Potassium currents are implicated in the generation of the cardiac impulse in the pacemaker cells in the SA node as well (Figure 3).

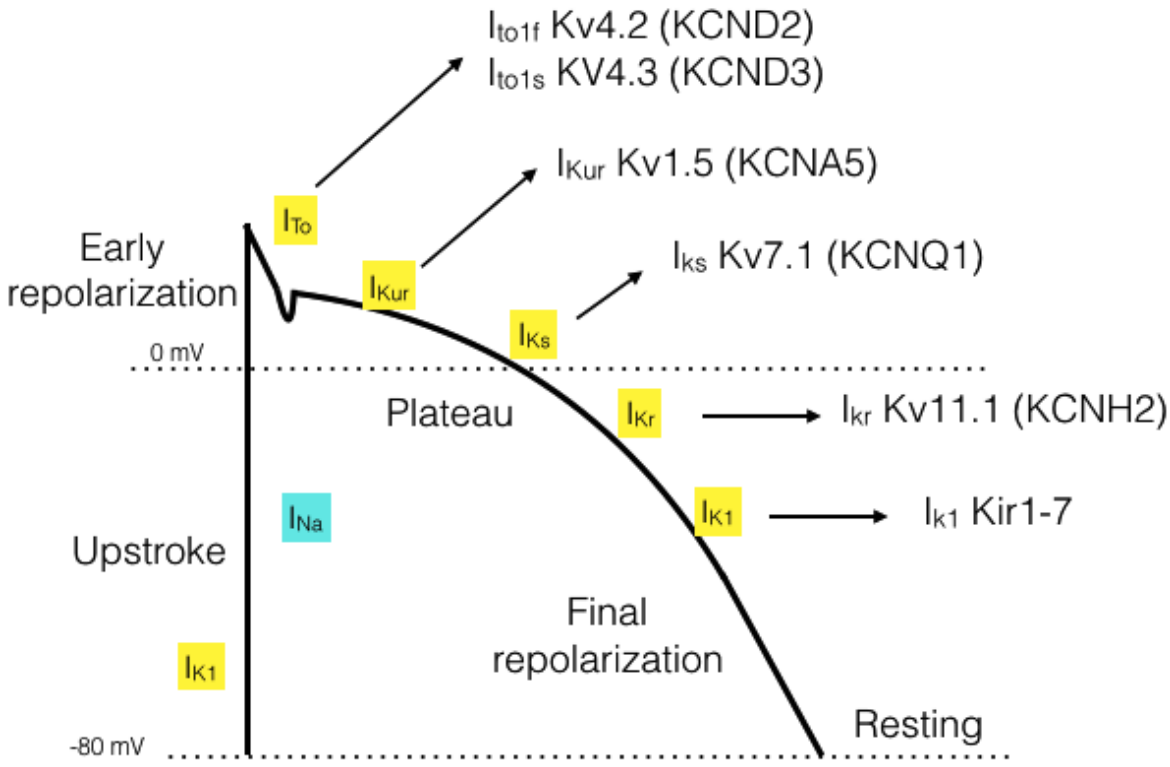


Figure 3. Cardiac action potential (non-pacemaker cell). Main ionic currents in relation to the phase of the action potential, the channels generating them and the genes codifying them. See text for details. Image of the Author's own design.

What are the cerebral counterparts of the cardiac potassium channels?

In the central nervous system (CNS) voltage-gated potassium channels play a central role as well. They regulate the duration of the neuronal action potential, the release of the neurotransmitters, and modulate the excitability and firing pattern of neuronal cells.
Several subtypes of voltage-gated potassium channels within the CNS have been described so far.

K_v1 channels are predominantly localized on axons and nerve terminals; K_v2 and K_v4 channels are expressed in the somatodendritic domain; K_v3 channels are expressed either in dendritic or in axonal domains, depending on the specific cell type; neuronal K_v7 channels (KCNQ) are predominantly found at axon initial segments and at the nodes of Ranvier, but a presynaptic localization of these channels has also been indicated by pharmacological studies.
Interestingly, five members of the KCNQ gene family have been identified. They can form homomeric or heteromeric potassium channel and are largely diffused in the CNS, contributing to the setting of the resting membrane potential of neuronal cells, and preventing their repetitive firing. These channels are basally opened at sub-threshold voltages and are inhibited by acetylcholine acting through muscarinic receptors coupled to the potassium channel itself.

Mutations of KCQN channels are associated with a variety of clinical conditions of different clinical impact [18].

KCNQ2 mutations, for instance, can both cause a benign condition such as benign familial neonatal convulsions and a severe disease with a progressive neurological impairment, leading to death, the so-called *KCNQ2* - related epileptic encephalopathy.

Of note, another member of this family of voltage-gated potassium channels, KCNQ1, is both expressed in the brain and in the heart and so is Kv11, or the "HERG" - channel. In the brain, this channel is widely expressed and helps set the frequency and the discharge stability of neurons. It also modulates the excitability of dopaminergic and GABAergic neurons.

As for cardiac cells, neurons do possess several inwardly-rectifying K channels as well. Seven major subfamilies have been identified so far. Some of them are implicated in the maintenance of the resting membrane potential, whereases others are needed for the potassium ions to keep cycling across the membrane itself.

Mutations of theses channels have been described as the origin of several epileptic and psychiatric disorders.

C3. Calcium channels

Cardiomyocytes possess two types of calcium channels, the L-type and the T-type, which transport calcium ions into the cells.

Calcium channels are structurally similar to sodium channels, being formed by 5 subunits (alpha1, alpha2, beta, gamma and delta).

The T-type channels predominate on the surface of pacemaker, atrial and Purkinje cells.

The L-type Calcium ion channel both activates and inactivates at more positive membrane potential (-30 mV) and inactivates more slowly than the T-type calcium channel, which indeed activates and inactivates at more negative membrane potential (-60 mV) and is more transiently open. This is reflected by a different molecular structure. The alpha1 subunit marks the difference between the two types of channels: the apha1c subunit, which forms part of the L-type calcium channels, possess a much larger carboxy-terminus, which is implicated in the Calcium-induced inactivation and in the regulation of the channel by protein kinases.

C4. **Ion channel mutations and electrical diseases: the concept of channelopathy**

Channelopathies are heterogeneous group of disorders resulting from the dysfunction of ion channels located in the membranes of all cells and many cellular organelles [19]. The term introduces a new way to look at previously known diseases such as long QT syndrome, Brugada syndrome or GEFS+.

The concept of channelopathy indeed underlines two important points.

First of all, it remarks that the centre of the pathology lies in the genetic mutation of an ion channel: the resulting perturbation of the ionic currents across the cellular membrane is therefore the ultimate responsible for the clinical symptoms that a given patient presents. While this appears as a very specific approach to each of the clinical conditions that the term "channelopathy" icludes, in that it directly refers to their underlying molecular mechanism, it is actually not.

Introducing the term channelopathy in clinical medicine has been a way of rather calling for a more holistic approach to conditions that have been previously dealt with in an ultra-specialistic way, and this is the second reason why the term channelopathy may be regarded upon as a sort of revolution for clinicians. Ion channels are only partially expressed in a tissue-specific manner throughout electrically-active organs.

This means that a mutation affecting an isoform of a particular ion channel may actually involve, for example, the copies of that channel located both in the heart and in the CNS at the same time. Clinical signs of the altered functioning of the mutated channel at both levels must be then taken into account and possibly foreseen (Table 4).

MAIN CHANNELOPATHIES IN THE HEART	MAIN CHANNELOPATHIES IN THE BRAIN
SCN5A: LQTS3, Brugada syndrome, nonprogressive familial heart block, paroxysmal familial ventricle fibrillation type 1, progressive familial heart block type IA (Lenègre-Lev syndrome), sick-sinus syndrome type I (AR), familial atrial fibrillation type 10, atrial standstill, dilated cardiomyopathy type 1E (NaV1.5) **SN4B**: LQTS (NaVbeta4)	**SCN2A**: Benign familial infantile epilepsy (NaV2.1) **SCN8A:** Cognitive Impairment with or w/out cerebellar ataxia (NaV1.6) **SCN1A**: Dravet Syndrome (NaV1.1) **SCN2A**: Early Infantile epileptic encephalopathy type 11 (NaV2.1) **SCN1A:** Familial hemiplegic migraine type 3 (NaV1.1) **SCN1B:** GEFS+ (NaVbeta1) **SCN4A**: Hypokalemic periodic paralysis type 2 (NaV1.4) **SCN4A**: Potassium-aggravated myotonia (NaV 1.4) **SCN9A**: Primary erythermalgia (NaV1.7) **SCN9A:** Paroxysmal extreme pain disorder (NaV1.7)
KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2, KCNJ5: LQTS (Kv7.1, Kv11.1, voltage-gated Isk-related subfamily member 1 and member 2, Kir2.1, Kir3.4)	**KCNQ2, KCNQ3**: benign familial neonatal seizures (Kv7.2/7.3) **KCNQ2**: Early infantile epileptic encephalopathy type 7
KCNH2, KCNQ1, KCNJ2: Short QTS (Kv11.1, Kv7.1, Kir2.1)	**KCNJ2**: Andersen-Tawil syndrome (Kir2.1)
KCNQ1, KCNE2, KCNA5, KCNJ2: Familial atrial fibrillation (kv7.1, voltage-gated Isk-related subfamily member 2, Kv1.5, Kir2.1)	**KCNA1**: episodic ataxia (Kv1.1)
	KCNJ10: EAST/SeSAME Syndrome (Epilepsy, Ataxia, Sensorineural deafness, and Tubulopathy/SEizures, Sensorineural deafness, Ataxia, Mental retardation Electrolyte Imbalance (Kir4.1)

Table 4. The main cardiac and neuronal channelopathies known to date. Note the involvement of the same gene in very different diseases. Table of the Author's own design.

C5. Channelopathies and structural disease: evidence in the heart.

Ion channels, as proteins, not only play a role in regulating the passage of ions across cellular membranes, but possess an intrinsic structural role as well.

Cardiomyocytes are both structurally and functionally interconnected at their longitudinal edge via a specialized protein complex that is called "intercalated disc", which is in turn composed by adherens junctions, desmosomes, and gap junctions (Figure 4).

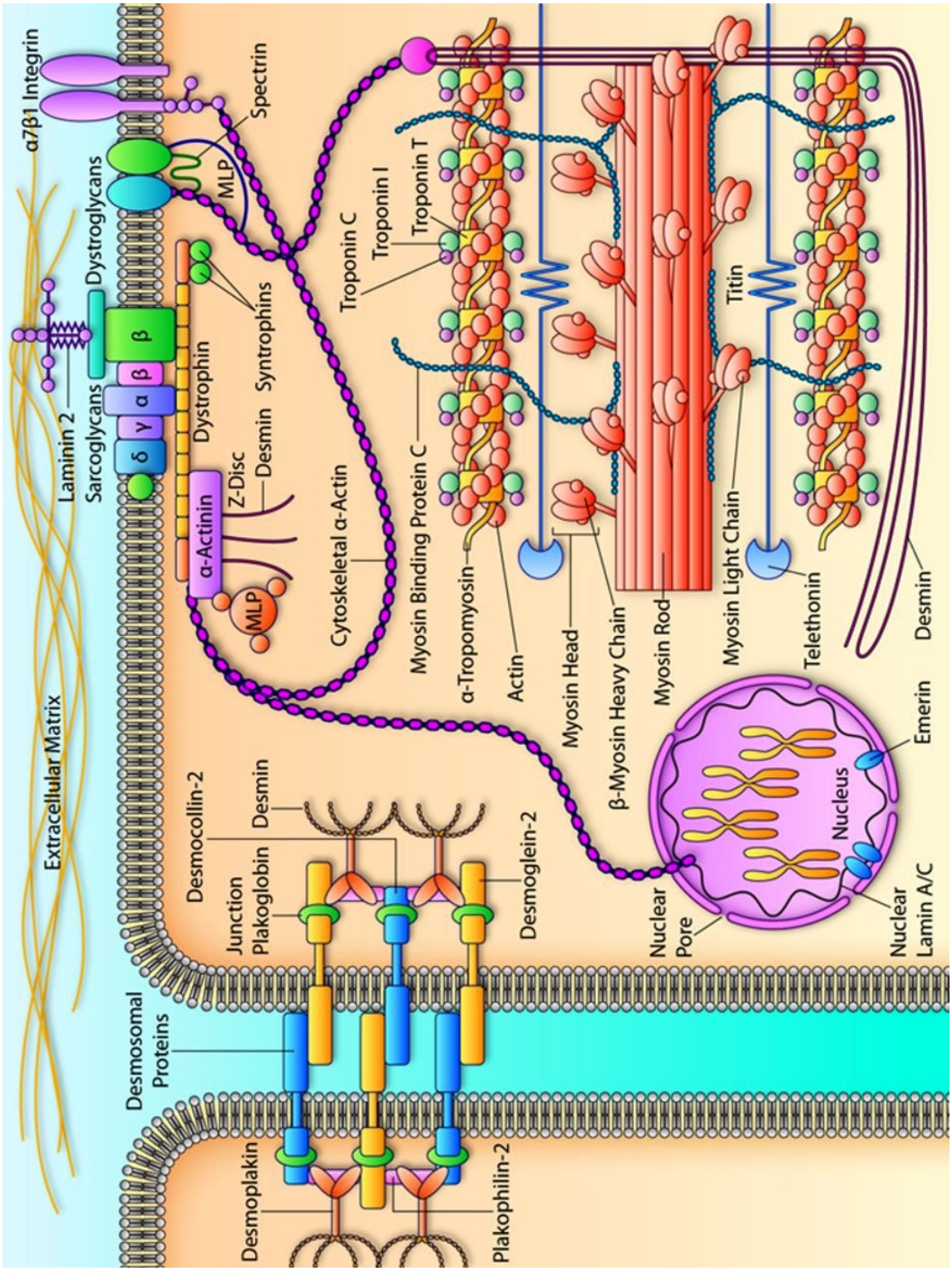


Figure 4. The net integrating intra- and extracellular proteins. From: Bezzina CR, Lahrouchi N, Priori S. Genetics of Sudden Cardiac Death. Circ. Res. 2015;116:1919-36. Reproduced with permission of the Editor. doi: 10.1161/ CIRCRESAHA.116.304030

Let us examine these three protein complexes [20]

1. Adherens junctions serve as an anchor point for myofibrils. The most important protein that characterizes this structure is alpha-catenin, which binds to the filaments of actin of the cardiomyocyte.
2. Desmosomes consist of an intercellular region, where the most important proteins are desmoglein-2 and desmocolin-2 and an intracellular region, where the most important proteins are plakoglobin, which binds to cadherins, plakophilin-2 and desmoplakin, which in turn binds to the intermediate filaments. Interestingly enough, recent studies have pointed out that a decreased expression of plakophilin-2 facilitates the appearance of ventricular arrhythmias after the injection of flecainide in a mouse model with PKP2-haploinsufficiency (PKP2-Hz), whereas in vitro studies demonstrated that in those cardiomyocytes completely lacking PKP-2 I_{Na}, i.e. sodium current, significantly decreased [21]. Therefore, it is though that the integrity of the intercalated disk is needed for sodium current to be efficiently set up in the cardiomyocytes and that there is a tight relationship between the structural and the functional characteristics of the proteins interacting within the intercalated disk (Figure 5).

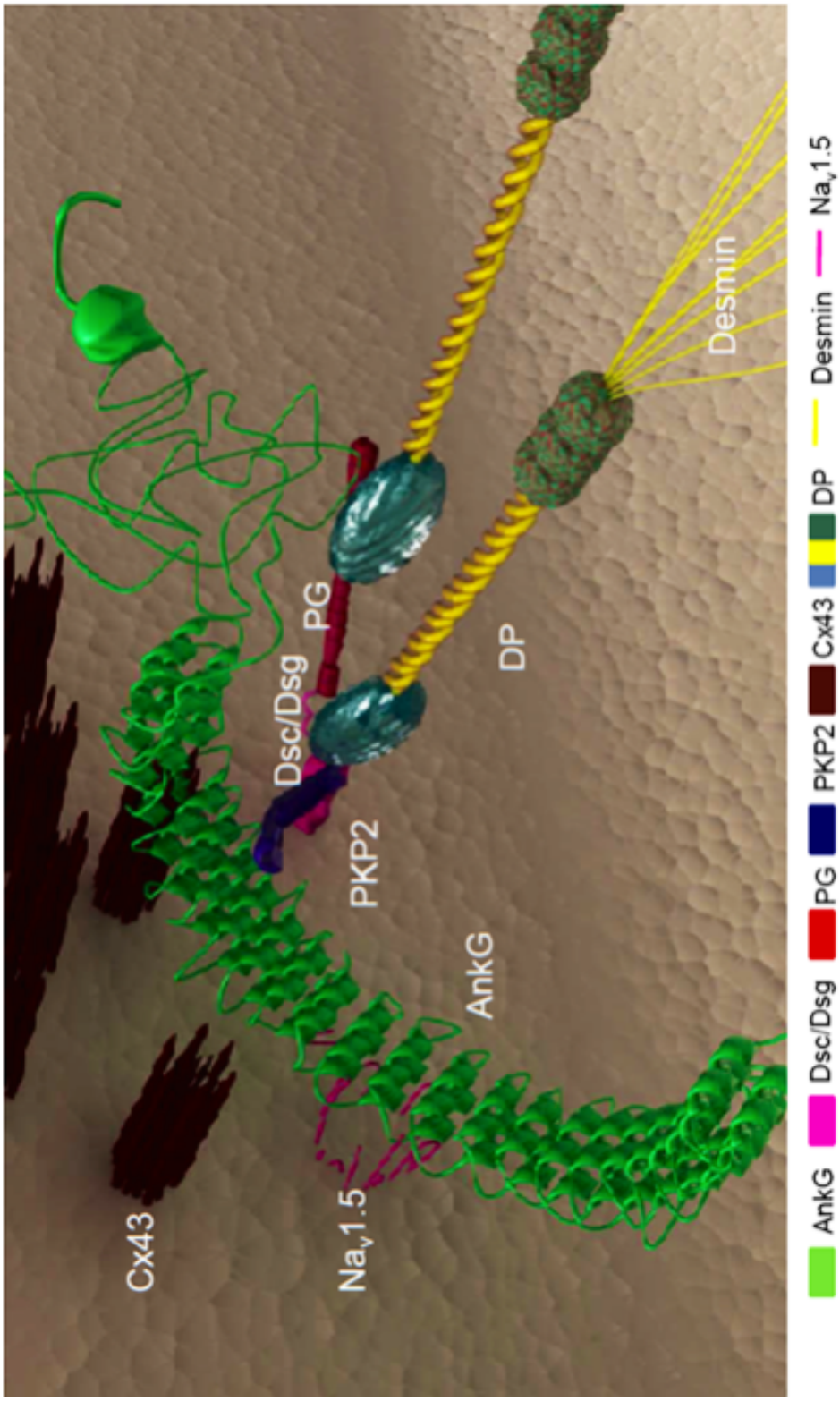


Figure 5. The relation between connexosomas, gap-junctions and NaV1.5. From: Cerrone M. Delmar M. Desmosomes and the sodium channel complex: Implications for arrhythmogenic cardiomyopathy and Brugada syndrome Trends Cardiovasc Med. 2014;24(5):184-90. Reproduced with permission of the Editor. http://dx.doi.org/10.1016/j.tcm.2014.02.001

3. Gap junctions. Classically, gap junctions have been thought to just serve as passive ionic openings between cells. They are abundant at the level of intercalated discs and relatively scarce at the lateral cell border of cardiomyocytes, which makes electrical impulse propagation intrinsically anisotropic. Each gap junction is formed by a couple of connexons, which are hexamers made up of a protein called connexin, weighing 43 kD (Cx43). The interesting data is that cardiac sodium channels have been demonstrated to preferentially localize at the intercalated discs, and that a reduction in the expression of Cx43 leads to an altered expression of the sodium channels, which is in turn arrhythmogenic by nature. Therefore, Cx43 does not only play a mere structural role, but has important functional characteristics as well. Indeed, its loss of expression, whether pre- or post-translational, is responsible for a loss of ionic current circulating between cells from one hand, and for a disruption in the amount of charge that is generated by the excited cells from the other one.

For all the above reasons, some diseases determined by the mutation of one of the proteins located at the intercalated disc should not be regarded upon as completely separated entities, but rather two aspects of same spectrum of pathology, like Brugada syndrome and arrhythmogenic cardiomyopathy (AC or ARVC or ARVD).

The first one is often generally referred to as a “pure channelopathy” in that it is thought to be a disease of the ionic current, mostly but not exclusively ascribed to mutations of the sodium channel in a structurally normal heart, whereas the second one is deemed to be a cardiomyopathy, namely a disease with structural abnormalities of the muscular walls of the right, and sometimes of the left ventricle as well.

However, various studies, like the one by Catalano and colleagues [22] have demonstrated that the hearts of patients affected by Brugada syndrome actually display an unexpectedly high rate of structural abnormalities when studied with cardiac MRI. In particular, they found out that these patients had a reduced contractility in the anterior-apical segment and in the outflow of the right ventricle when compared to healthy volunteers.

Moreover, they were able to demonstrate a significant enlargement of the right ventricular inflow, although that was not true at the outflow level (which had nonetheless previously observed in others studies, such as the one of Papavassiliu et al [23]) and no fibro-fatty replacement was observed through the MRI examination. Fibro-fatty replacement is usually indicated as a typical histological feature of ARVC and has actually been found at the time of post-mortem examination in patients that actually do meet the ECG criteria for Brugada syndrome [24].

For this reason, the group of Corrado, in Italy, has traditionally regarded Brugada syndrome and ARVC as part of the same spectrum and these studies seem to actually confirm this hypothesis. A more recent study [25] found out that the right ventricle of patients affected by Brugada syndrome was actually characterized by a higher collagen content, especially in the RVOT and the epicardium. Moreover, Cx43 expression in the RVOT of these patients was significantly decreased.

On the other hand, patients affected by ARVC do not necessarily die in relation to the degree of the dysfunction and the structural disruption that affects their heart. Sudden death may occur before, and may depend of the occurrence of ventricular fibrillation, with mechanisms that are similar to those described for patients affected by Brugada syndrome. Gomes and colleagues for instance [26] have pointed out that mutations in the desmoplakin are responsible for the mislocalization of connexin 43, which in turn may determine the appearance first of an electrophysiological disease and then, of an overly structural disease.

So taking into account all that has been previously commented, are there any other possible answers to the usual question regarding the differences between adults and children as far as the probability of diagnosing these genetically-determined diseases is concerned? Why, if the mutations causing Brugada syndrome and ARVC are present since

birth, are these diseases less probably - if ever - diagnosed during childhood?

There are several possible answers to this question. One possibility that would deserve further studies and that relates to what has just been illustrated about the intercalated discs, is that the structure of the discs themselves is not always the same throughout one person's life.

Vreeker and colleagues [27] studied the variations in the distribution of N-cadherin, Cx43 and NaV1.5 in human cardiomyocytes taken from 18 hearts of individuals who died from non-cardiovascular causes. Age of the specimens ranged from a gestational age of 15 weeks through 11 years postnatal. Using immunofluorescence, they found out that N-cadherin was concentrated at the region of the intercalated disc by age 2.5 years - implying that before that age the mechanical properties of the myocardium might be significantly different from the adult's - and that a similar behavior was observed as far as Cx43 was concerned as well. NaV1.5 tended to concentrate at the region of the intercalate discs much later, by age 7 years. Before that time it could be found at the lateral sides and within the cardiomyocyte as well.

The shift in NaV1.5 localization seems to be related to the change towards the fast, anisotropic conduction typical of the mature myocardium (Figure 6).

How these observations translate into the surface ECG characteristics of these patients has not been clarified yet.

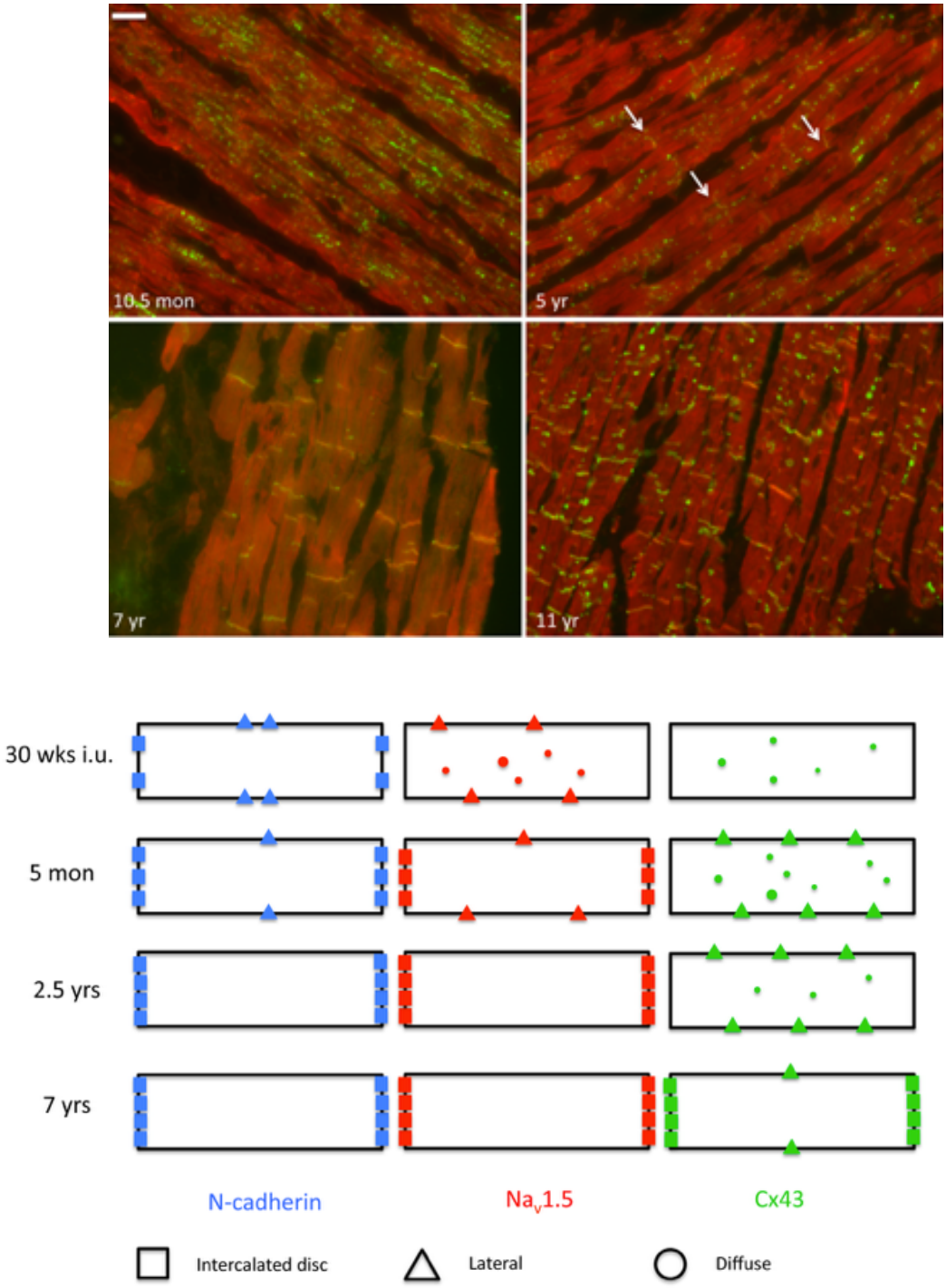


Figure 6. Above, immunofluorescence study of localization of Cx43 during life. Below, schematic representation of the immunofluorescence study of the N-cadherin, NaV1.5 and Cx43 localization in cardiomyocytes. From: Vreeker et al. Assembly of the Cardiac Intercalated Disk during Pre- and Postnatal Development of the Human Heart. PLoS One. 2014;9(4):e94722 **Copyright:** © 2014 Vreeker et al. Open-access article. All Credits to the original publication. doi: 10.1371/journal.pone.0094722

D. The ECG in childhood. Markers of arrhythmogenic risk and structural disease

D1. QT duration: On the surface ECG the QT interval represents the sum of the duration of the ventricular depolarization and repolarization. However, most of the electrophysiological significance of the duration of the QT interval lies in its relationship with cardiac repolarization.

A prolongation of this phase of the action potential reflects in a prolonged QT, and since the repolarization phase depends on outward potassium currents, on persisting inward sodium current (I_{Na}), and on slow inward calcium current, it becomes clear that the mutations that are actually responsible for the majority of long QT syndrome (LQTS) cases are those determining a loss of function of the outward potassium current or a gain of function of the sodium or calcium currents. In 90% of patients, the affected genes are indeed KCNQ1, KCNH2 and SCN5A, causing respectively LQTS1, LQTS2, LQTS3.

As may be expected, a prolonged repolarization alters the T-wave morphology as well. T wave morphology may actually help diagnose LQTS. T waves which look broad-based are often observed in LQTS1, biphasic T waves are common in LQTS2 and a late-appearing T waves may be seen in LQTS3.

The variability of refractoriness among cardiomyocytes with prolonged repolarization intervals in which adrenergic stimuli cause the release of calcium ions from the endoplasmic reticulum, which in turn originates the so-called post-potentials, may be at the base of re-entry arrhythmias in LQTS.

At the very beginning of the study of electrocardiography, the QT interval was surprisingly not deemed to be important. With the description of the first cases of long QT syndrome by Jervell and Lange-Nielsen at the end of the 1950s, it became apparent that measuring the length of the QT on the surface ECG was actually relevant, but deciding whether a given subject's QT interval is too long may not be so straightforward [28].

First of all, one has to decide the optimal lead where the QT should be measured. For historical reasons, this is usually lead DII; however, this often results to be a good choice for another - and more important - reason: as the electrical axis of the heart in most subjects is oriented along lead DII, this is often the lead where measuring the length of the QT interval results the most accurate. In the case it was not possible, suitable alternatives may be V5, V6 or DI.

Another question is deciding where the T wave actually ends. On the surface ECG, this may be a difficult task, either because the T wave itself may not be well defined or because of the presence of a U wave, which should not be considered part of the QT interval. The most widely accepted way to establish the end of the QT segment on the surface ECG is the one proposed by Lepeschkin and Surawicz back in 1952, the so-called tangent-method, in which end of the T-wave is defined as the intersection of the tangent to the descending limb of the T-wave with the baseline (Figure 7).

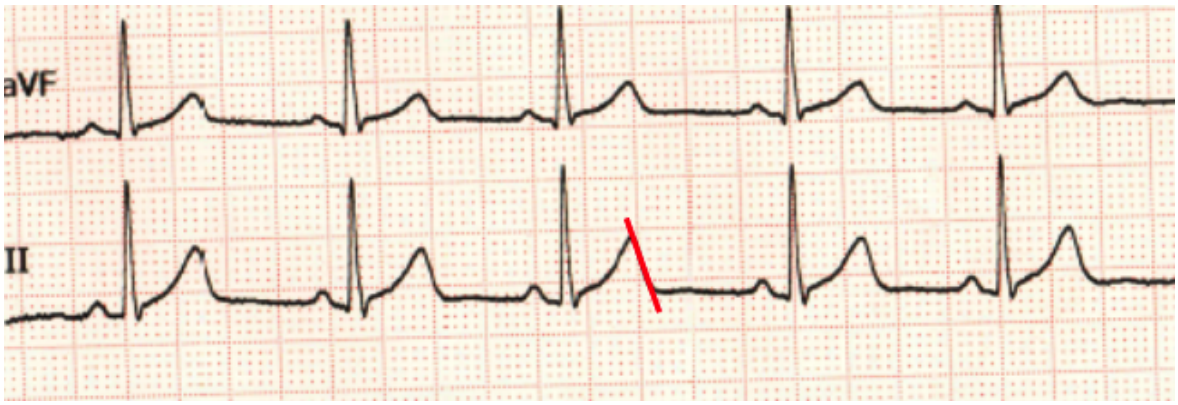


Figure 7. An example of calculation of the QTc using the so called tangent method. The end of the QT segment on the II lead is determined as the point of intersection of the tangent to the descending limb of the T-wave with the baseline. ECG of one of the patients of the study population.

A third problem is that in a normal subject, the QT duration varies depending on the heart rate, so that the QT duration needs to be corrected accordingly. How is that done?

A variety of formulas has been employed, the Bazett's one, which was introduced in 1920, being the most widely used: the absolute QT duration expressed in msec is divided by the square root of the duration of the preceding RR interval. It is generally said that the Bazett's correction is less accurate at very slow or very fast heart rates (which would be the case of infant's normal heart rates, that are normally higher than 100 bpm even at rest). For this reason, other formulas have been developed, such has the Fridericia exponential correction, more accurate at faster heart rates, in which $QTc = QT/(RR^{1/3})$, and the linear Framingham method in which QTc is calculated as $QT + 0.154(1-RR)$.

Normal QT values depend upon sex and age [29]. The clinical context is important as well. In an ECG obtained for other reasons in a female patient, a normal value would be defined as between 360 and 460 sec and in a male patient, as 350 and 450 msec.

In prepubertal children, the usual cut-off is 440 msec.

In a patient screened for a family history of LQTS, a QTc of 430 msec or more would be considered pathological.

At 4 minutes into the recovery time of an exercise test, a QTc of at least 445 sec would be highly suggestive of long QT syndrome in an adult patient [30], but in children, as Berger and coworkers pointed out in a cohort of 94 healthy boys and girls aged 8 to 17 years, the 98th percentiles of the QT interval at minutes 4 to 6 of the recovery phase varied between 482 to 491 ms, and the 95th between 480 and 483 msec. Values beyond these ones would not been expected within this age range [31].

Still, it seems that the most important problem related to the measurement of the QT interval is that even though it can be normal on a 12-lead ECG, there is an overlap between patients affected by long QT syndrome and normal controls. In other words, it is not possible to exclude that a subject has LQTS syndrome on the basis of a normal ECG and no single cut-off may be used alone to diagnose long QT syndrome [32]. For this reason, Schwartz et al. elaborated a score in 1993, updated in 2006 [33], aiming at defining the probability of a subject of being affected by LQTS on the basis of a variety of elements; the actual QTc duration on the surface ECG is just one of them.

The score consists of ECG findings (QTc duration, 4-minutes QTc duration after exercise test, evidence of torsade de pointe, notched T waves in 3 leads, bradycardia for age), elements drawn from the

subject’s clinical history (previous syncope with or without coincidental stress), congenital deafness, elements taken from the subject’s family history (definite LQTS diagnosis, unexplained cardiac death). Each of these elements are rated according to their relevance for the diagnosis of LQTS, being a QTc >480 msec the only element given 3 points per se. If the total score is at least 3.5, the diagnosis of LQTS may be done (Table 5).

Schwartz score for LQTS

ECG	
QTc	
> 480 msec	3
460 - 479 msec	2
450 - 459 (male) msec	1
4 - min recovery QTc after exercise test ≥ 480 msec	1
Torsades de pointes	2
T - wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age	0.5
Clinical history	
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family History	
A. Family members with definite LQTS	1
B. Unexplained sudden cardiac death age < 30 among immediate family members	0.5

Diagnosis is made with total score ≥ 3.5 in the absence of a secondary cause for QT prolongation

Table 5. Schwarzt score to diagnose LQTS. Table of the Author's own design.

Short QT syndrome is far less frequent than LQTS and only recently described [34]. Five variants have been reported up to now, according to the causative mutations.

On a molecular level, the implicated mechanism is either an increase of the outward potassium current or a defect of the inward calcium current, both of which result in a reduction of the duration of the repolarization, and therefore, of the duration of the QT interval. SQTS4 and SQTS5 have been reported in less than 10 patients each, and co-exist with a Brugada phenotype.

A QTc measurement under 330 sec would be pathologically short in men and a 340 msec - QTc should be generally considered abnormally short in women, although 360 msec in men and 370 msec in women are potentially diagnostic cut-offs in those subjects who have a suggestive family or personal history.

Short QT syndrome has a high penetrance, and the most common clinical expression is cardiac arrest, even at a very young age. For this reason, and due to the relative rarity of the disease and the lack of clear triggers, the most accepted therapy for affected patients is the implant of an ICD. In those patients in whom this is not possible, quinidine seems to be the only acceptable pharmacological therapy, although its long-term efficacy has not been established.

Family history of atrial fibrillation is very common as well.

D2. QRS duration and morphology

A. QRS duration is a classical adverse prognostic factor in a variety of cardiac diseases. Even in the general population, the duration of the QRS complex is an independent predictor of sudden cardiac death, even when it is not associated with the typical morphology of bundle branch block [35].

B. Differential duration between right precordial leads and left precordial leads, also known as "parietal block" and defined as a QRS duration in V_1-V_3 that exceeds the duration of the QRS complex in lead V_6 by >25 ms, is one of the diagnostic criteria for arrhythmogenic right ventricular dysplasia (ARVD) [36]. Another way of expressing a differential duration of the depolarization phase between the right and the left ventricle in these patients is the ratio of the QRS duration in the right and left precordial leads ($V_1+V_2+V_3$/ $V_4+V_5+V_6$). When this ratio is equal to 1.2 or greater, it is considered to be another diagnostic criterion of ARVD. More recently, an S-wave upstroke (defined as the interval calculated between the nadir of the S wave and the isoelectric line, between V_1 and V_3) of 55 msec or more was found in up to 95% of subjects with ARVD in a study examining the ECG characteristics of 50 patients with such a disease [37]. Again, these observation were made on ECG tracings obtained

in adults, and data in children and adolescents are basically scarce or completely absent in the cardiovascular literature. This partly depends on the fact that ARVD has been considered as a progressive disease, without clinically and electrocardiographically recognizable manifestations up to the adult age in most cases. The traditional ECG characteristics, as they were originally defined by the Task Force in 1994 [38] such as the persistently negative right precordial T waves beyond age 12 preclude per definition the diagnosis in children although this concept has been challenged [39].

C. Voltage. QRS represents the ventricular depolarization phase and as such, the amplitude of the complex is related to the mass generating the depolarizing current. For this simple reason, one way to evaluate the probability of ventricular hypertrophy is to rely on the measurement of the QRS amplitude on the surface ECG. For children, the normal criteria were classically set by Davignon in 1978 [40], although in 2001 Rijnbeek [41] defined new references for the pediatric ECG. In clinical practice, the reality is much more complex, as the diagnosis of left ventricular hypertrophy based solely on electrocardiographic criteria is one of probability, and it should take into account not only the QRS amplitude, but other ECG characteristics as well, as cardiologists generally do in the adult setting: QRS axis, QRS duration, delayed intrinsecoid deflection, P

wave characteristics, morphology of the repolarization (ST segment deviation and T wave axis), as in the Romhilt-Estes point score system. In a study published in 2015, Bratincsák et al. [42] analyzed the ability of the ECG to predict left ventricular hypertrophy based on the Davignon and Rijnbeek criteria and according to the classical Sokolow-Lyon index (S in V_1+R in V_5 or V_6 - whichever is larger - ≥35 mm and R in aVL ≥11 mm) and Cornell index (S in V_3+R in aVL ≥28 mm in men or ≥20 mm in women) among others in a population of 250 patients, in whom an echocardiographic study was then performed. The Authors found a positive predictive value of the ECG criteria of only 29-50%, concluding that the ECG ability to predict left ventricular hypertrophy in children is far from being satisfactory. Right ventricular hypertrophy seems to be an even more complicated issue for the physician interpreting pediatric ECGs. In 1993, 434 ECG of children older than 3 months were examined by Fretz and Rosenberg to identify the most reliable ECG criteria of right ventricular hypertrophy [43]. They concluded that a positive T wave or "qR" pattern in V_1 are highly specific but insensitive markers of RVH in children and that, in the presence of an incomplete right bundle branch block, the "rSR'" pattern is a relatively sensitive but nonspecific predictor of RVH. More recently, the same problem was approached by Puchalsky et al [44] in a retrospective study in which the classical ECG criteria of right ventricular hypertrophy were tested

as a screening test for echocardiographic right ventricular hypertrophy. The ECG criteria that the patient needed to meet included at least one among: a) R-wave V1 >98th percentile for age; b) S-wave in V6 >98th percentile for age; c) upright T wave in V1 in patients <10 years; d) rSR’ pattern in V1 (with R’ >15 mm in infants younger than 12 months or >10 mm in older children and e) qR pattern and V1. The echo criteria that were assessed included tricuspid regurgitation velocity and diastolic right anterior ventricular wall thickness. Retrospectively the ECG criteria resulted to have a good specificity (82%) and a good negative predictive value (84%), but demonstrated significant limitations as a screening tool for RVH when used alone. However, over the very last years the ECG has remained an essential screening test in various setting for its accessibility and the interest for new diagnostic indexes of left ventricular hypertrophy in particular keeps being high. Brothers and colleagues [45] elaborated in 2014 a pediatric-specific ECG criteria (R in aVL+ S in V_2 >23 mm) to screen for left ventricular hypertrophy, demonstrating a superior sensitivity in children (aged between 7 to 21 years) presenting with a genetic mutation for hypertrophic cardiomyopathy when compared with traditional, non-pediatric specific ECG criteria, and an overall superior specificity.

D. QRS morphology**.** An interesting aspect of QRS morphology is fragmentation, which can be defined as the presence of an additional

R wave (R’) or notching in the nadir in the nadir of the S wave, or the presence of >1 R’ in two contiguous leads, corresponding to a major coronary artery territory [46]. Fragmented QRS has been recognized as an adverse prognostic factor in the case of coronary artery disease, in arrhythmogenic right ventricular cardiomyopathy (in which the number of leads with fQRS has been associated to the severity and extension of the disease), in patients with Ebstein’s anomaly and Fallot’s tetralogy and in those with Brugada syndrome. In patients with Brugada syndrome, SCN5A mutation was found more frequently in those patients that have fQRS in their ECG [47]. The electrophysiological basis of fQRS are probably to be sought in its ability to reflect inhomogeneous depolarization due to myocardial fibrosis, such as in the case of coronary artery disease or corrected tetralogy of Fallot. fQRS may also be the electrocardiographic expression of regional variations of the upstroke of the action potential or myocardial fibrosis - and this might happen in as in the case of Brugada syndrome as well. The prevalence of fQRS in healthy children with no known heart disease has not been systematically studied. See Figure 8 and 9 for examples.

E. Delta-wave. The natural history of this form of pre-excitation diagnosed during childhood has been studied by Cain and colleagues [48]. Sudden cardiac death was a rare event at presentation (0.2%)

and during follow-up, especially if no structural heart defect was present (1.1 per 1,000 patient-years). Syncope represented the first symptoms in 4% of the cohort (446 children). In 35% of cases, pre-excitation naturally disappeared during follow-up.

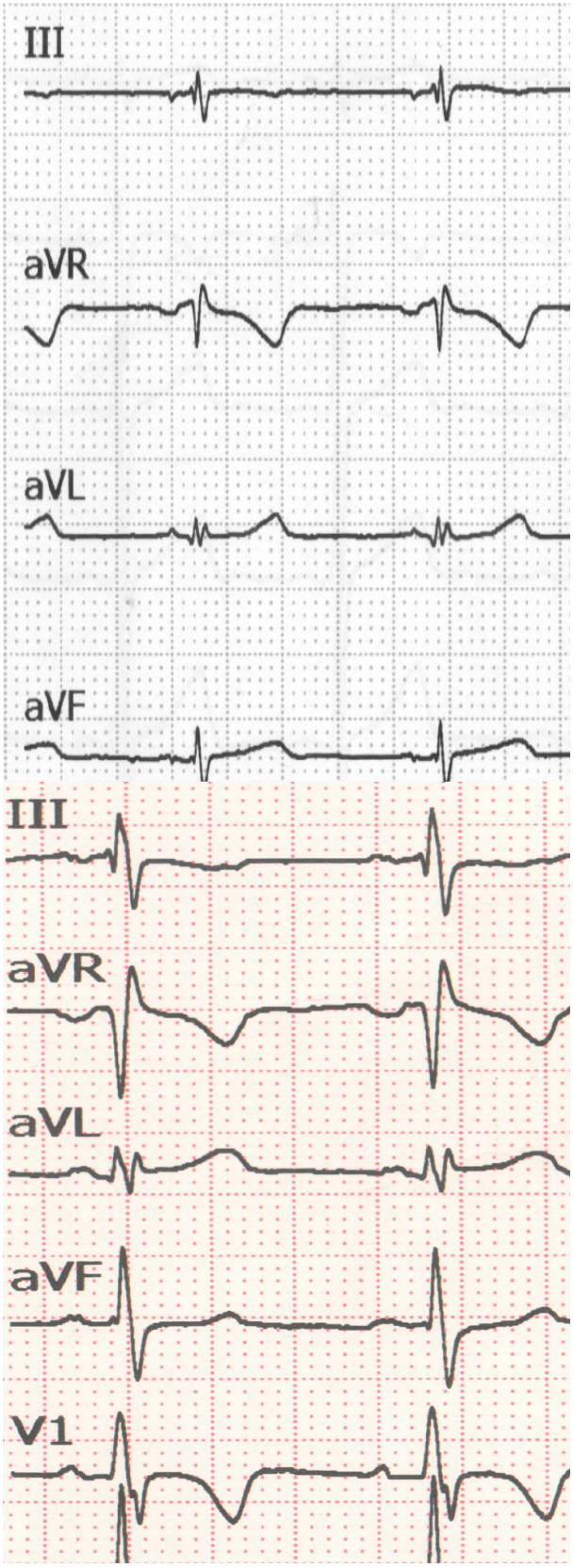


Figure 8 Varieties of fragmented QRS (fQRS) from our own study population. See the following chapter for comment.

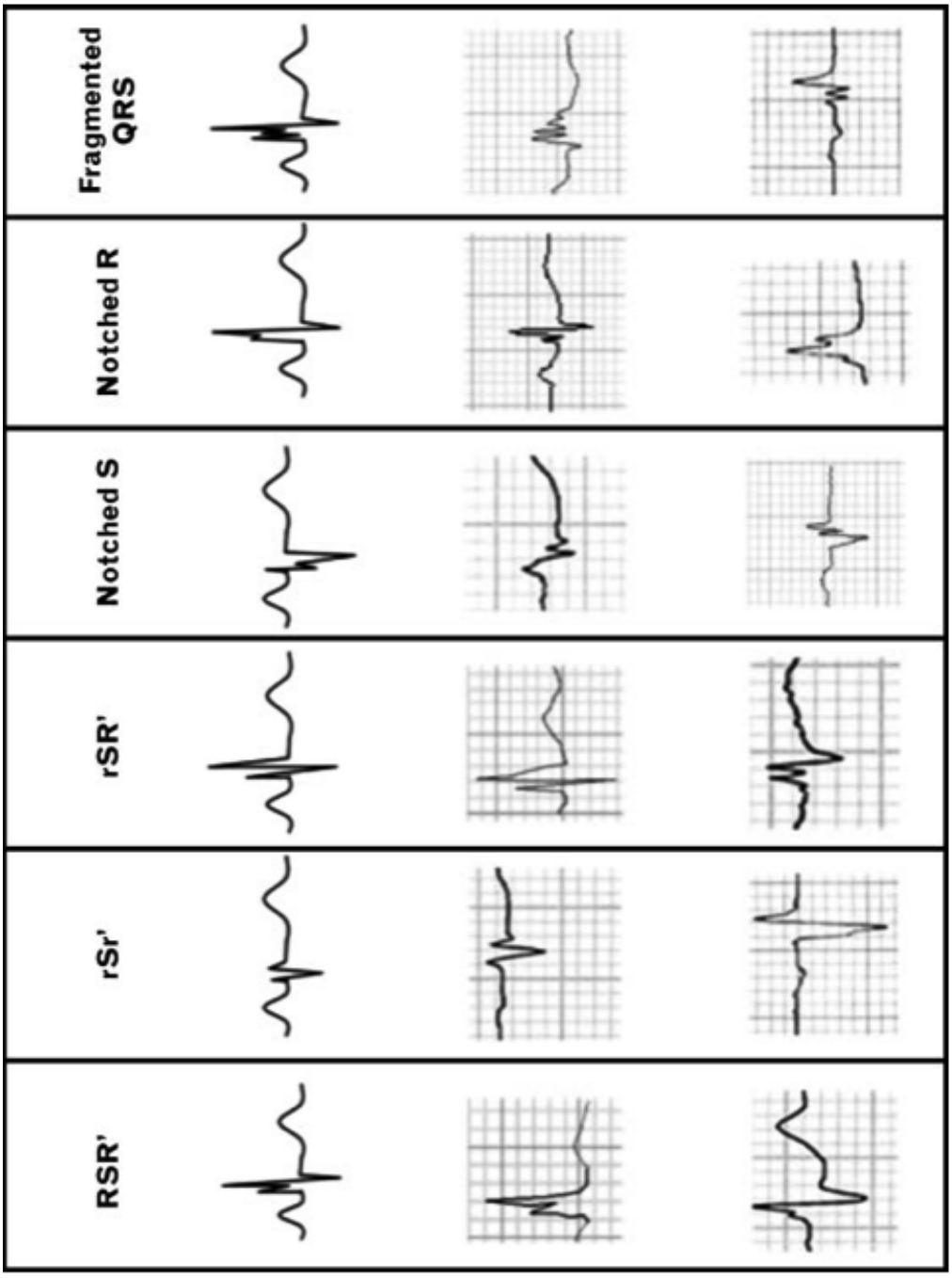


Figure 9 Varieties of fragmented QRS (fQRS). From: Das MK, Zipes DP. Fragmented QRS: A predictor of mortality and sudden cardiac death. Heart Rhythm 2009;6(3 Suppl):S8-14. Reproduced with permission of the Editor. doi: 10.1016/j.hrthm.2008.10.019

D3. QRS-T wave angle: It is the angle between the main direction of depolarization and the main vector of repolarization. The widening of the QRS-T wave angle on the frontal plane expresses a divergence of the vectors of depolarization and repolarization which may depend on a structural or electrical abnormality that alter their normal sequence.

In the adult population the QRS-T wave angle on the frontal plane is generally considered pathological when ≥100° [49,50,51], in neonates and children less than 3 months when it is ≥30°, in children older than 3 months when it is ≥60°. Generally speaking, a QRS-T wave angle wider than 90° is surely pathological in children older than 3 months.

D4. T wave: In neonates aged 1-3 days T waves are usually positive throughout V1-V3. The persistence of positive T waves between V1 and V3 after the first week of life should rise the suspicion of a structural abnormality. On the other hand, the persistence of negative T waves between V2 and V3 after the 12-16 years of age should prompt further investigations [52]. Bifid T wave in lead V2 and V3 are considered a normal variant in children, especially between age 5 and 8 [53]. It is considered a transitional phenomenon, not normally found in adults. Bifid T waves in older children or in leads other than V2 and/or V3 should be considered abnormal. Long QT syndrome (LQTS) may occasionally be associated with T-wave abnormalities, such as notching

of broad-based T-waves in 3 or more leads in LQTS1 and biphasic T-waves in LQTS2.

D5. Early-repolarization (ER): this ECG variant is defined by an elevation of the J point (i.e., the QRS-ST junction) manifested either as a terminal QRS slurring or notching (i.e., a positive deflection inscribed in the terminal aspect of the QRS complex) associated with a concave upward ST-segment elevation or prominent T waves in at least two contiguous leads.

This pattern is approximately found in 10% of the general population and for many years has been regarded as a benign electrocardiographic variant. However, in the last years, some papers have pointed out that early-repolarization may actually be associated with an increased risk of ventricular fibrillation [54]. The localization of the ER pattern could have prognostic implications as well. Case-control studies have associated in particular sudden cardiac death to ER in inferior and lateral leads. Furthermore, in inferior leads, the most important prognostic factor seems to be the amplitude of the ST-elevation.

It is believed that ER is due to an endo - epicardial gradient occurring during the phase 1 of the action potential, corresponding to the notch of the action potential itself [55].

D6. ST segment: the importance of the ST segment in the ECG interpretation lies mainly in the fact that it has to be isoelectric. It represents a phase of the cardiac cycle when there should be no electrical gradient, that is to say, no net ionic current through the ventricular surface nor between the endo- and epicardial surfaces; this coincides with the plateau phase of the action potential, and takes place between the ventricular depolarization and repolarization phases. In the heart, these processes follow a precise sequence justifying the aspect of normal ECG: the endocardium depolarizes before the epicardium but repolarizes afterwards, so that the QRS axis and the T wave axis should always be concordant in the same lead. Moreover, the left side of the septum depolarizes first, followed by the right aspect of the septum itself, the apex, and, finally, the free walls.

When all these conditions are not met, the ST segment is not isoelectric any longer and the T wave and QRS wave axis are not concordant on the surface ECG. The typical situation in which this may happen is myocardial ischemia, either due to a primary obstruction of the coronary arteries or to an increase in the oxygen requirements of the myocardial muscle, as it may be seen the case of an acute pulmonary embolism.

Brugada syndrome deserves a special mention in the setting of our study, as its typical features are an abnormal ST segment and T wave in

the right precordial leads. Three patterns have been described, although only one is diagnostic per se.

Type 1 is diagnostic of Brugada syndrome and is characterized by a coved, 2-mm (0.2 mV) ST-segment elevation followed by a negative T wave. Brugada syndrome is definitively diagnosed when this pattern is observed in a patient with documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at 45 years old or less, coved-type ECGs in family members, inducibility of VT in the setting of an electrophysiological study, syncope, or nocturnal agonal respiration (clinical criteria were withdrawn in the 2013 consensus to improve diagnostic power [56]).

Type 2 Brugada pattern has a “saddleback appearance”, which consists of a high takeoff ST-segment elevation of 2 mm, a central depression consisting of a 1-mm ST elevation, followed by either a positive or biphasic T wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of less than 1 mm. Type 2 and type 3 ECG are not diagnostic of Brugada syndrome per se.

The consensus on the Brugada syndrome [57] suggests that placement of the right precordial leads in a superior position (up to the second intercostal space above normal) can increase the sensitivity of the ECG

for detecting the Brugada phenotype in some patients. Interestingly, the latest papers [58] on the Brugada syndrome have suggested that the basic electrophysiological anomaly of the syndrome would lie in a delayed depolarization of the right ventricular outflow (RVOT, which, the region that is best depicted by displacing upwards the right precordial leads), causing a gradient that would be responsible for the the ST-segment elevation in the right precordial leads during the depolarization of the right ventricle (when the inflow region and the right ventricular chamber would be more positive than the outflow region); the same gradient would then persist during the repolarization phase, when the RVOT is supposed to repolarize later, justifying therefore the negative T-wave in the same leads. A very recent in vivo and in vitro study by Nademanee et al. [25] seems to further support this theory.

D7. Epsilon wave: the epsilon wave is observed in up to 30% of patients with right ventricular arrhythmogenic dysplasia (ARVD). It consists of a low-magnitude positive deflection appearing in V1 and V2 just after the QRS complex. Epsilon waves are generally believed to be a quite specific sign of the disease, representing late depolarizations arising in the structurally abnormal right ventricle of the affected individuals. It is anyway an electrocardiographic sign that should not be relied upon to screen patients for ARVD, as it appears late during the development of the disease.

Chapter 2.

The study

THEORETICAL JUSTIFICATION FOR THE STUDY

On the basis of what has been previously discussed in the "Introduction" section, the following points and unanswered questions emerge:

- The incidence of arrhythmias and arrhythmogenic syndromes presenting as febrile or nonfebrile seizures in children is unknown;
- Thus, it is not yet possible to come to accurate conclusions about the true incidence of such conditions in children;
- For the same reason, it is not possible to exclude the fact that the observed higher incidence of arrhythmogenic diseases such as Brugada syndrome in adults compared to children depends on an intrinsic evolution of the syndrome (for instance, because of a progression of an underlying structural abnormality) or on a different adaptation of the organism to an event such as an arrhythmia, i.e. the same event may present itself as a febrile seizure in a child and as a cardiac arrest in an adult;
- Until now, however, no study has systematically simply described the electrocardiographic features in children with febrile, nonfebrile seizures or syncope;
- Given the previous points and the fact that some evidences of the most recent literature make us suggest that the ECG characteristics

of a channelopathy might have an evolutive nature, it might be useful to systematically follow the patients in which any suggestive abnormalities are identified.

Unanswered Questions:

1. How many cases of fever or febrile seizure in children may be the clinical presentation of arrhythmia?
2. How many children attended to for syncope have an abnormal ECG tracing?
3. If the electrical activity of the brain in some individuals tends to suddenly deteriorate resulting in seizures, what happens to the electrical activity of the heart of these subjects, since these two organs share similar ion channels?
4. Does the systematical performance of an ECG in children attended to in the Emergency Department for seizures or syncope change the clinical management of these patients?

AIMS OF THE STUDY

- To systematically describe the electrocardiographic characteristics of pediatric patients admitted to an emergency department of a tertiary hospital for febrile generalized seizures, generalized nonfebrile seizure or syncope;
- To describe the clinical characteristics of the study population, and to evaluate the possible relations with ECG characteristics of the patients included in the study.

MATERIALS AND METHODS

A. Study design

The present study is an observational descriptive cross-sectional study.

All patients included in the study went through a thorough physical examination, along with a 12-lead ECG in the Emergency Department. Personal and family history and clinical data were collected at the time of patient's assessment in the Emergency Department or after making posterior phone contact with the patient's family if necessary.

An ECG was performed at the time of admission and interpreted by the Emergency physician for clinical decisions.

The electrocardiographic records were saved and subsequently evaluated by two independent investigators of the Pediatric Cardiology Service.

B. Target population

All pediatric patients aged between 0-14 years (included) who came to the Emergency Department with a presumptive diagnosis of syncope, generalized seizure or in a postictal state after a generalized seizure episode were included.

C. Location and duration of the study

The study was conducted in the Emergency Department at Children's Hospital of La Paz, Madrid, in collaboration with the Pediatric Cardiology Department of the same centre for 1 year, subsequently extended to 18 months.

C.1 Inclusion criteria

Patients aged between 0 and 14 years (included) who come to the Emergency Department and that:

- Had presented a generalized convulsive episode as previously defined (febrile or nonfebrile);
- Had presented a syncopal episode as previously defined;
- Presented in a post critical state with prior history of seizure;
- And for whom a written informed consent signed by the parents (for children aged less then 12 years old) was obtained.

In those cases in whom the patient was a child aged 12 years or more, a written assent of the patient him or herself had to be obtained as well.

C.2 Exclusion criteria

- Patients with structural neurological disease (tumors, hemorrhage, stroke, hydrocephalus ...) that may cause a seizure;

- Seizures secondary to an acute disorder of the central nervous system, including meningitis, encephalitis, drug intoxication and drugs;
- Focal seizures;
- Patients with known electrolyte disorders;
- Patients with congenital heart disease (excluding the following: atrial septal defect, ventricular septal defect, and not - hemodynamically significant patent ductus arteriosus);
- Hemodynamic instability, either primary or resulting from another condition (i.e., septic shock, hypovolemic shock);

D. Selection of the study sample

The chosen method was that of consecutive sampling, so that all pediatric patients who came to the Emergency Department during the time of the inclusion and that presented the appropriate clinical characteristics were asked to participate to the study.

E. Study variables

In every patient the following clinical, demographic and electrocardiographic variables were recorded.

i) Demographic variables

(1) Age: Defined in months and days

(2) Gender: Male (M) // Female (F)

ii) Qualitative categorical variables:

The presence or absence of the following variables was analyzed:

(1) Palpitations: defined as the subjective feeling of heartbeat acceleration;

(2) Tonic movements: defined as sustained muscle contractions measured in seconds/minutes when possible;

(3) Clonic movements: defined as involuntary, sudden, regularly repetitive, brief contractions of a muscle or muscle group;

iii) Quantitative continous variables:

(1) Blood pressure: systolic and diastolic. Measured with a blood pressure cuff on the right arm, using an appropriate cuff size for the child. The measure was expressed in mmHg, when possible;

(2) Heart rate: obtained during physical examination or during the ECG recording and expressed in beats per minute (bpm);

(3) Body temperature (°C) obtained with axillary thermometer at the time of the ECG recording, classifying patients as febrile (>37.5°C and nonfebrile <37.5°C);

(4) Duration of convulsive episode: duration of the convulsive episode, in minutes, if reported by the ER physician.

iv) Qualitative categorical variables:

The presence or absence of these variables in relatives of 1st and 2nd grade will be analyzed:

(1) Syncope (as previously defined);

(2) Pre-syncope: defined as a sense of impending loss of consciousness, without losing consciousness;

(3) Arrhythmias: defined as any type of heart rhythm disorder followed by specialized medical care;

(4) Sudden death: defined (in this study) as sudden and unexpected death of unknown cause;

(5) Aborted sudden death: defined (in this study): as a sudden and unexpected need for resuscitation maneuvers in absence of which the person would have died;

(6) Epilepsy: defined as a chronic disease characterized by recurrent, unprovoked seizures (clinical manifestation of an abnormal and excessive discharge of a group of brain neurons) (≥2).

v) ECG realization and analysis:

(1) Realization technique: in the Emergency Department a standard 12-lead ECG in each case meeting the inclusion criteria. Standard parameters were chosen (paper speed 25 mm/sec and amplitude of 1 mV=10 mm). The leads were placed according to the standard scheme (Figure 10):

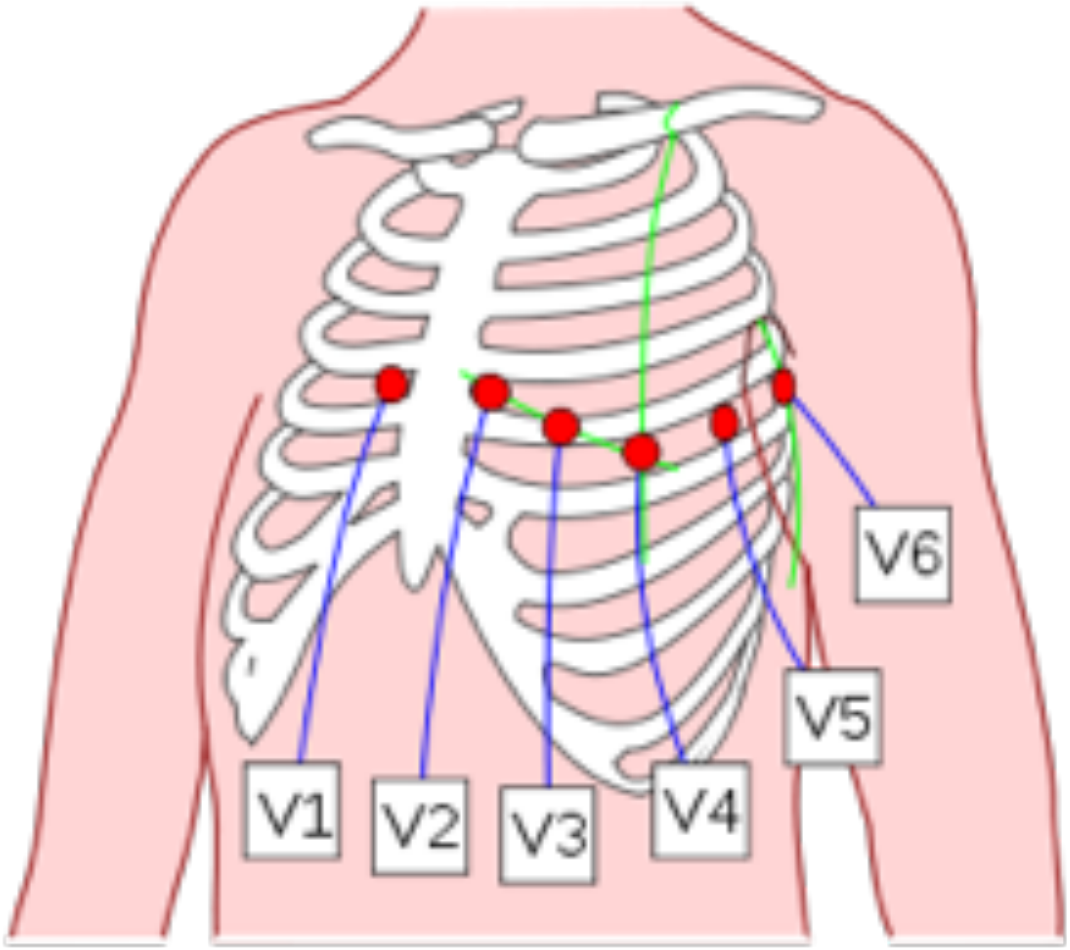


Figure 10. ECG realization technique. Placement of the precordial leads**.**

Limb leads:

RA (right arm), red lead: right wrist;

LA (left arm), yellow lead: left wrist;

LL (left leg), green lead: left ankle;

RL (right leg), black lead: right ankle.

Precordial:

V1: 3rd intercostal space along the right sternal border;

V2: 3rd intercostal space along the left sternal border;

V3: the midpoint between V2 and V4;

V4 5th intercostal space left in the middle clavicular line;

V5: 5th left intercostal space in the anterior axillary line;

V6: 5th left intercostal space at the mid-axillary line.

(2) Interpretation of ECG recording:

(A) sinus rhythm: YES/NO. Defined by the presence of QRS complexes that are all preceded by a P wave that is positive in leads I and aVF.

(B) Presence of ventricular enlargement: YES/NO. If this voltage criteria or Cornell or Sokolow rates are met.

- Sokolow Index: voltage of the S wave in lead V1 + voltage of the R wave in lead V5 ≥35 mm.

- Cornell Index: voltage of the S wave in lead V3 + voltage of R wave in lead aVL≥20 mm.

(C) T-wave axis (according to technique defined by Aro and coworkers [51]) and QRS-T wave angle on the frontal plane;

(D) ECG intervals (all expressed in milliseconds) were compared with reference tables for comparison;

- PR interval: the interval between the start of the P wave and the onset of the following QRS complex;

- QRS interval: between the start of the Q wave and the end of the S wave. If the interval is greater than normal QRS morphology is defined;

- J point elevation (YES/NO): J-point elevation measured in mV in V1 and V2;

- Presence of early repolarization: YES/NO (defined as J-point elevation of 1 mm or more concave ST segment or S wave notch in two 2 or more leads between V2 and V6);

- Absolute QT interval: calculated between the start of the Q wave and the end of the T wave according to the tangent method. The most appropriate leads to calculate the QT interval should be considered DII and V5, or, in alternative, the lead that allows the best definition of the QT duration in the tracing is of poor quality;

- Corrected QT (QTc) using Bazett's formula: QTc is obtained by dividing the absolute value of the QT interval and the square root of

the absolute value of the previous RR interval, according to the Bazett's formula. A QTc ≥0.45 s will be considered pathologically long (with exceptions as commented in the introductions) and a QTc <0.33 s pathologically short;

- QT dispersion and QTc dispersion, defined as the difference between the maximum value (QT max and respectively QTc max) and the minimum value (QT min and respectively QTc min) measured in the same electrocardiogram;
- ST segment deviation, measured in V1, V2, V3, V4, V5 and V6 (expressed in mm);
- Ratio R/q in aVR.

Ethical considerations and use of personal data

1. The clinical trial has not implied the realization of any invasive interventions on the patients. It has not interfered with the realization of the appropriate treatment for the included patients;

2. Prior to the realization of the electrocardiogram, information about the trial to the child's parents has been provided for their informed consent to be obtained;

3. Patients' data have been collected and processed anonymously;

4. The responsibility for indicating the realization and the first interpretation of the ECG has been the treating physician's;

5. If the result of the realized ECG could determined a variation in the treatment originally foreseen for the patient, such a variation was communicated to the patient's family by the professionals involved in the research and/or by the treating physicians in order to arrange an accurate evaluation in the the Cardiology Department, both as a completion of the study protocol and for ethical reasons.

PART 2.

Chapter 3.

Statistical methods

Given the size of the samples, comparisons between continuous variables within subgroups was made using the Mann-Whitney U-test to avoid making the assumption that the distribution of values was normal.

Chi-square test was used to test associations between categorical variables when subgroups were composed by at least five units.

Pearson correlation coefficient calculation was used to measure the strength of linear association between continuous variables of the original study sample.

Continuous variables were expressed either as mean±standard deviation or as median (max; min values) as appropriate.

Software used for calculations included: Numbers (Apple Inc.), and on-line statistic calculators (socscistatistics.com).

Chapter 4.

Results

A. Demographic characteristics of the population

A total of 75 patients were enrolled in the studied. Patients who had presented with pre-syncope (no loss of consciousness), or had either a known structural neurological (n=2) or cardiac disease (n=1) were excluded. Incomplete tracings (n=1), absence of any clinical history (n=2) or of any tracing (n=1) were other reasons for exclusion.

40% of the included patients were females. Mean age was 6.35±4.81 years (Median 4.44; Min 0.36; Max 14.86).

B. Clinical data

28 patients were admitted to the Emergency Department with a diagnosis of syncope (=37.3% of the included patients). In 26 cases the presumptive diagnosis was vagal syncope. In 2 cases syncope occurred in the context of exercise. In 50% of cases patients had already had a previous syncopal episode.

22 cases of febrile seizures were observed, 13 of which represented the first episode occurring to the patient.

The rest of cases (n=25, 33.3% of total), were represented by nonfebrile seizures.

The cases of nonfebrile seizures were clinically defined as follows:

- 23 cases of primary generalized seizures;
- 2 cases of secondary generalized seizures;

- No cases of absences were included in these study.

16 (64%) represented a first episode of seizure; 9 (36%) were a recurring seizure.

In all cases presenting for a seizure, the patient had never been previously studied by means of an ECG.

Family history was taken at the time of the ED visit or by telephone interview in 28% of cases.

In the family history of one of the patients that were attended to in the context of this study there was a case of sudden death.

12.7% patients presenting for any type of seizure had a family history significant for seizures, and 20% patients attended to for a febrile seizure had a family history significant for seizures of any type.

As per policy of the hosting Institution, Patients presenting for their fist seizure were admitted for hospital observation. One patient was subsequently transferred to the Pediatric ICU for a worsening of her neurological condition.

Clinical data and data obtained from family history are summarized in Table 6.

	Patients with syncope	Patients with febrile seizures	Patients with nonfebrile seizures
Number (% of total)	28 (37.3)	22 (29.3)	25 (33.4)
Mean age (months) (min; max)	119.3 (20.9; 178.8)	25.7 (11.6; 54.3)	69.8 (0.4; 171.6)
Previous episodes of syncope (n, %)	14 (50)	0	0
Previous episodes of febriles seizures (n, %)	0	7 (31.8)	5 (20)
Previous episodes of nonfebrile seizures (n, %)	0	0	1 (4)
Family history of seizures (n, %)	2 (7.1)	2 (9.1)	4 (16.0)
Family history of arrhythmias (n, %)	5 (18)	1 (4.5)	0
Family history of sudden cardiac death (n, %)	1 (3.5)	0	0
Family history of epilepsy (n, %)	4 (14.2)	1 (4.5)	3 (12.0)
Family history of syncope (n, %)	6 (21.4)	2 (9.0)	8 (32.0)

Table 6. Clinical data and familial history of the study population divided into subgroups according to the diagnosis at presentation.

C. Electrocardiographic data

A 12-lead ECG was performed at the moment of physical examination in each case.

The ECGs were subsequently interpreted by the attending physician in the Emergency Department for decision making and later recollected by the investigators for a second evaluation.

Each ECG was examined by two investigators (D.C. and M.O.M.) blind to each other's observations.

ECG data were compared with normal references for gender and age.

When the investigators found an abnormal ECG, they contacted with the patient's family to arrange a complete clinical and instrumental evaluation in the Cardiology outpatient clinic with one of the investigators (M.O.M.), who was responsible for deciding the priority and the nature of the evaluation in the outpatient clinic.

The clinical history was also taken into account for such a decision (i.e.: syncope during effort).

The main electrocardiographic results are summarized in Table 7.

Number	Diagnosis	ECG findings	Age (years)
1	nonfebrile seizure	Cornell index 23. QRS fragmentation	1.85
2	nonfebrile seizure	Sokolow index 36. Cornell index 32, PHI 24, QRS fragmentation	10.89
3	febrile seziure	Cornell index 22, QRS fragmentation	1.92
4	febrile seizure	Sokolow index 39	2.48
5	syncope	Sokolow index 37, PHI 25, QRS fragmentation	12.42
6	nonfebrile seizure	Horizontal QRS axis. Altered repolarization phase. QRS fragmentation	0.36
8	nonfebrile seizure	QTc abnormally long. Altered repolarization. QRS fragmentation	12.61
11	febrile seizure previous nonfebrile seizures	Short PR; prominent P wave. Altered repolarization phase.	1.69
13	syncope. previous syncopes	Abnormal QRS/T angle; Altered repolarization phase, QRS fragmentation.	7
14	nonfebrile seizure	Cornell index 21	1.42
15	syncope	Altered repolarization phase, QRS fragmentation	7.81
19	syncope	Non sinus rhythm, QRS fragmentation	7.21
20	nonfebrile seizure	Slightly prolonged PR interval. QRS fragmentation	4.19
21	síncope vs nonfebrile seizure	Cornell index 24. QRS fragmentation	10.02
23	nonfebrile seizure	Altered repolarization phase	1.60
25	syncope	Sokolow index 38	9.81
26	febrile seizure	Altered repolarization phase; Abnormal QRS/T angle. fragmented QRS	2.71
27	syncope	Mild elevation of the ST segment in V1-V2-V3, QRS fragmentation.	7.99
28	febrile seizure	QRS axis abnormal for age; altered repolarization phase.	1.39
30	syncope	Mildly prolonged PR interval right intraventricular conduction delay, QRS fragmentation.	9.65
31	syncope	Abnormal QRS/T angle; altered repolarization phase.	2.36
34	febrile seizure	Cornell 22, altered repolarization phase; undetermined QRS axis	0.97

36	seizure; nonfebrile previous febrile seizures	Prolonged QTc, altered repolarization; unspecific intraventricular conduction delay, QRS fragmentation, PHI 27	12.38
44	febrile seizures	Altered repolarization phase. abnormal QRS/T angle.mildly short PR interval	1.43
46	syncope	Leftward deviation of the QRS axis. QTc in the upper limit.	13.51
48	syncope	Sokolow index 38. biphasic T wave in V2 and V3	13.76
49	febrile seizure	Pediatric Hypertrophy index 30	1.44
50	febrile seizure	Mildly elevation of ST segment in V1 small Q wave in aVL lead	2.63
51	syncope with effort previous syncopes	Non sinus rhythm. Early repolarization; R/S in V1 upper limit for age, fragmented QRS	12.91
52	nonfebrile seizure	Q wave in the inferior leads; QRS fragmentation	1.73
54	febrile seizure	Abnormal QRS/T angle	2.88
57	febrile seizure	Non sinus rhythm; Cornell 26	4.44
64	febrile seizure	Abnormal QRS/T angle. Abnormal T wave in right precordial leads. Horizontal QRS axis (abnormal for age)	1.29
65	syncope	short PR without clear delta wave	13.14
66	syncope	Abnormal QRS/T angle; altered repolarization phase. Prolonged QTc, fragmented QRS.	13.59
69	syncope vs nonfebrile seizure	Sokolow index 41 pediatric hypertrophy index 23, early repolarization pattern QRS fragmentation	14.33
70	syncope with effort	QRS fragmentation in aVF, DIII, V1 Altered repolarization (biphasic T wave in V2-V3 and flattened T wave in aVF).	11.90
71	syncope	pure R wave in V1, early repolarization	14.85
72	syncope	negative T waves V1-V3, flattened T waves in other leads, QRS fragmentation	12.92
73	nonfebrile seizure	QRS axis abnormal. Non sinus rhythm.	8.09
75	syncope	Sokolow index 35; hyperacute T waves	10.56

Table 7. Main ECG findings. Isolated fragmentation of the QRS is not reported. PHI: Pediatric Hypertrophy Index. As an amend to the original protocol, Cornell index is reported in this study as pathological in males if ≥28, as per literature.

D. Analysis of the results

a. Clinical characteristics of the study population

The study population is a representation the typical pediatric population attended to in the Emergency Department for an episode of loss of consciousness. It is important to remark that in at least three cases, it was not possible to immediately determine if the episode was a sincope or a crisis and the final diagnosis was reached after joined evaluation by neurologists and cardiologists.

b. ECG characteristics

b1. **Rhythm** The large majority of the patients in our study presented sinus rhythm. Sinus arrhythmia was considered to be a normal variant, and was not differentiated from sinus rhythm for the purposes of this study. One isolated ventricular ectopic beat was observed. One patient presented one atrial ectopic beat in his ECG tracing; one other presented a right low-atrial rhythm, and had presented to the Emergency Department for a syncopal episode. Two cases of left atrial rhythm were also observed.

b2. **Intervals**

PR: Only one child presented a short PR segment, even though there was no visible delta wave. No AV block was observed in the studied population.

QRS: 11 patients presented a true incomplete right bundle branch block (rR'), which is a common feature of the ECG in the young, provided that no other pathological features (such as a Brugada-like repolarization) are present.

One patient presented a left-axis deviation, which is also described as a criterion per se of left anterior hemiblock. This patient did present a mild mitral insufficiency, but her mitral valve was described as normal. Follow-up was assured.

No complete left-bundle branch blocks were observed.

QTc: This was the most concerning feature of the collected ECGs. Revision by the investigators allowed for detection of three patients with a pathologically elongated QTc in their first ECG. One of them presented a pathological repolarization as well. He presented to the Emergency Department for a loss of consciousness that was interpreted as of neurological origin (he had presented a tonic-clonic seizure), having been previously diagnosed with absences and seizures in relation with fever. This patient's ECG is displayed in Figure 11.

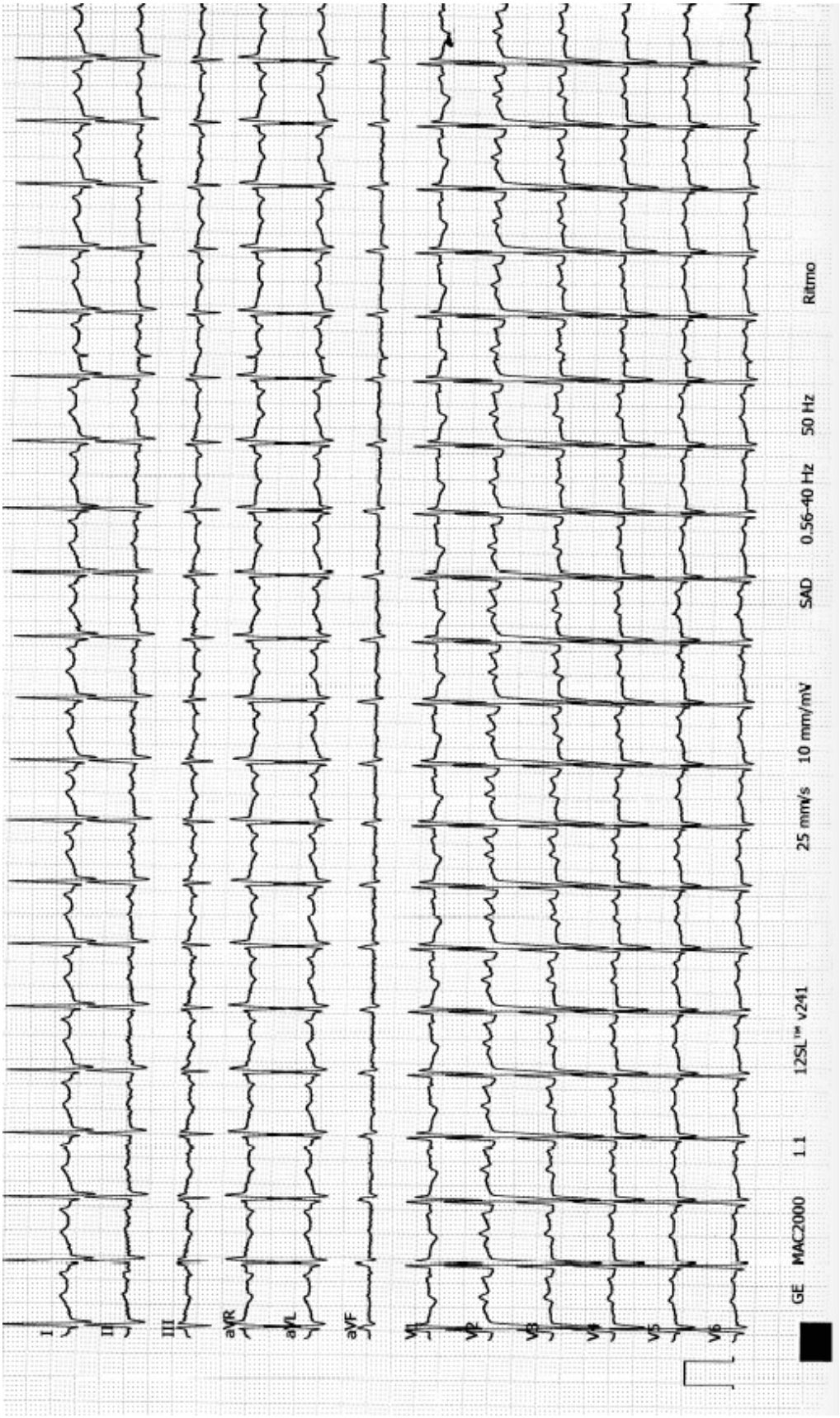


Figure 11. Patient 36's ECG. Note the alterations of the repolarization phase and the prolonged QTc.

The other patient, a female adolescent, had a previous history of “epilepsy”, and presented to the ER for a loss of consciousness. The QTc in the first ECG was 560 msec. Subsequent follow-up was assured. See Figure 12 to visualize the ECG.

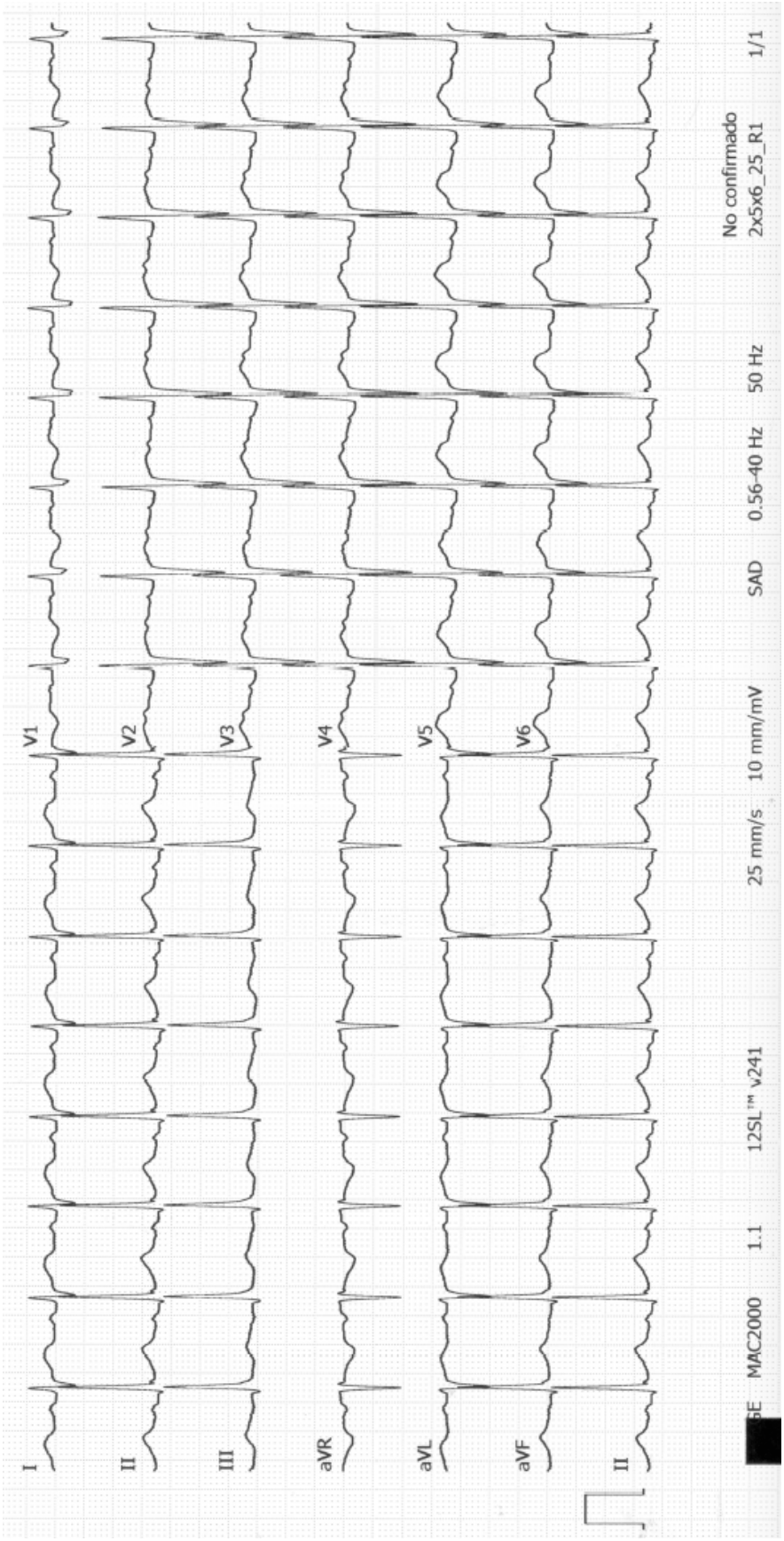


Figure 12. Patient 8's ECG. Note the the very prolonged QTc.

b3. **QRS voltages** Voltages were examined from various point of view in an attempt to identify pathological ECGs in the most accurate way.

- Voltage of the Q wave in the V6 lead: abnormal in 0 patients. However, one child aged 1.73 years presented an abnormal Q wave in the inferior-lateral leads in relation to the voltage of the QRS complex;
- Cornell index (*see note Table 7): abnormal in 7 patients;
- Sokolow index: abnormal in 7 patients;
- Pediatric Hypertrophy Index: abnormal in 5 patients.

It is important to remark that only a small number of patients (3) presented more than one abnormal hypertrophy index.

b4. **QRS fragmentation.** This feature is a "qualitative" aspect of the QRS complex. A chi-squared test was performed to evaluate if it was a more frequent finding in those patients that had already presented a previous episode of crisis or syncope or that had any family history of seizures, epilepsy, arrhythmia, sudden death. A chi-squared test yielded a p value of 0.1155, not significant at $p<0.05$. Results are summarized in Table 8. The frequency of QRS fragmentation was also compared in children attended to for the first episode of syncope or seizure versus recurrent seizures of any type or recurrent syncope. Again, no significant difference was noted (chi-square: 0.144, p value: 0.704, not significant at $p<0.05$). See Table 9 for details.

	any previous history	no previous history
Fragmented	26	7
Not fragmented	26	16

Table 8. Patients with fragmented QRS with personal or familial history of sudden cardiac death, epilepsy, arrhythmia, seizures versus patients with no history. Distribution of fragmentation between the two subgroups was compared by means of a chi-square test. Difference was not statistically significant at $p < 0.05$

	not first episode	first episode
Fragmented	14	19
Not fragmented	16	26

Table 9. Patients with fragmented QRS presenting for either the first episode of syncope or seizure or for a recurrent syncope or seizure. Distribution of fragmentation between the two subgroups was compared by means of a chi-square test. Difference was not statistically significant at $p < 0.05$

Fragmentation did not appear to be more frequent in patients presenting with a seizure as against those attended to for a syncopal episode. Chi-square test yielded a non significant result in this case (Chi-square statistic 0.6528, p-value 0.419) as depicted in Table 10.

Interestingly, fragmentation of the QRS complex was more frequently observed in patients with febrile seizures (either actual or previous). The difference was indeed statistically significant as per chi-square statistic as outlined in Table 11.

	any seizure	syncope
Fragmented	19	14
Not fragmented	28	14

Table 10. Patients with fragmented QRS presenting for syncope vs. any type of seizure. Distribution of fragmentation between the two subgroups was compared by means of a chi-square test. Difference was not statistically significant at $p<0.05$

	Febrile seizure	Nonfebrile seizure
Fragmented	13	5
Not fragmented	11	18

Table 11. Patients with fragmented QRS presenting for febrile seizures versus nonfebrile seizure. Distribution of fragmentation between the two subgroups was compared by means of a chi-square test. Difference was statistically significant at $p <0.05$ (chi-square statistic 5.226, p value: 0.0222)

b5. **Repolarization** Repolarization was analyzed from various points of view:

1. Presence of early repolarization (ER);
2. Abnormal QRS/T wave angle on the frontal plane;
3. QTc interval;
4. QT dispersion and QTc dispersion in the cohort;
5. Relationship between QRS/T wave angle on the frontal plane and QTc dispersion

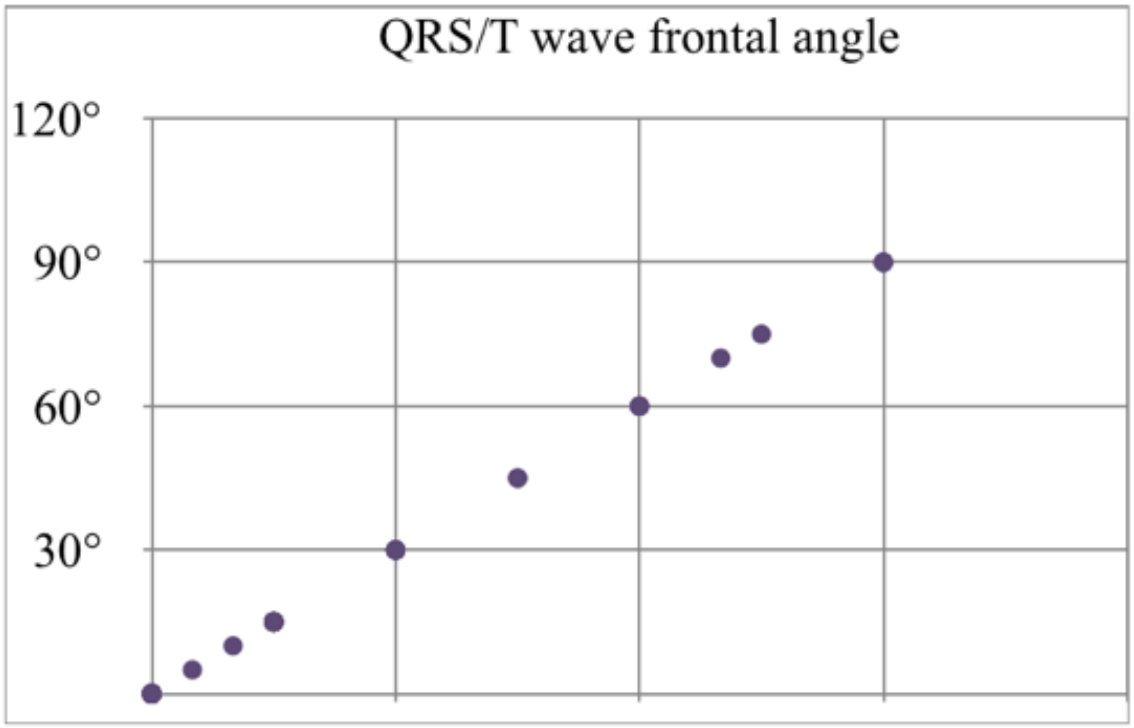
1. *Early repolarization* was a common finding in patients presenting for syncope (n=12, 42.8% vs. n=5, 10.6% in patients diagnosed with loss of consciousness of neurological origin). A chi-squared test was performed to evaluate if the difference was statistically significant (Table 12). The chi-square statistic is 10.391, being the p value 0.0012, and therefore significant at $p<0.05$.

	seizures	syncope
early repolarization	5	12
no early repolarization	42	16

Table 12. Patients with early repolarization (ER), and seizures or syncope. Distribution of ER between the two subgroups was compared by means of a chi-square test. Difference was statistically significant at $p<0.05$

2. QRS/T wave angle on the frontal plane. QRS/T wave angle was calculated in 72 cases. It was not possible to calculate it in three cases in which the QRS angle was defined undetermined. The overall mean QRS/T wave angle in our cohort was 18.42±26.23°, with 13.3% of patients presenting with an angle ≥60°. Of them, four (5.3%) presented with an angle≥90° (see Table 13). Comparison between the mean QRS/T wave angle of children presenting with febrile seizures or with a history of previous febrile seizure and those without did not result significant (Z-score -1.26, p-value 0.207) at $p<0.05$, as per Mann-Whitney U test, being the distribution of the values approximately normal.

Graph 1 summarizes the distribution of the QRS/T wave frontal angle within our cohort.



Graph 1. QRS/T wave frontal angle distribution in the study population

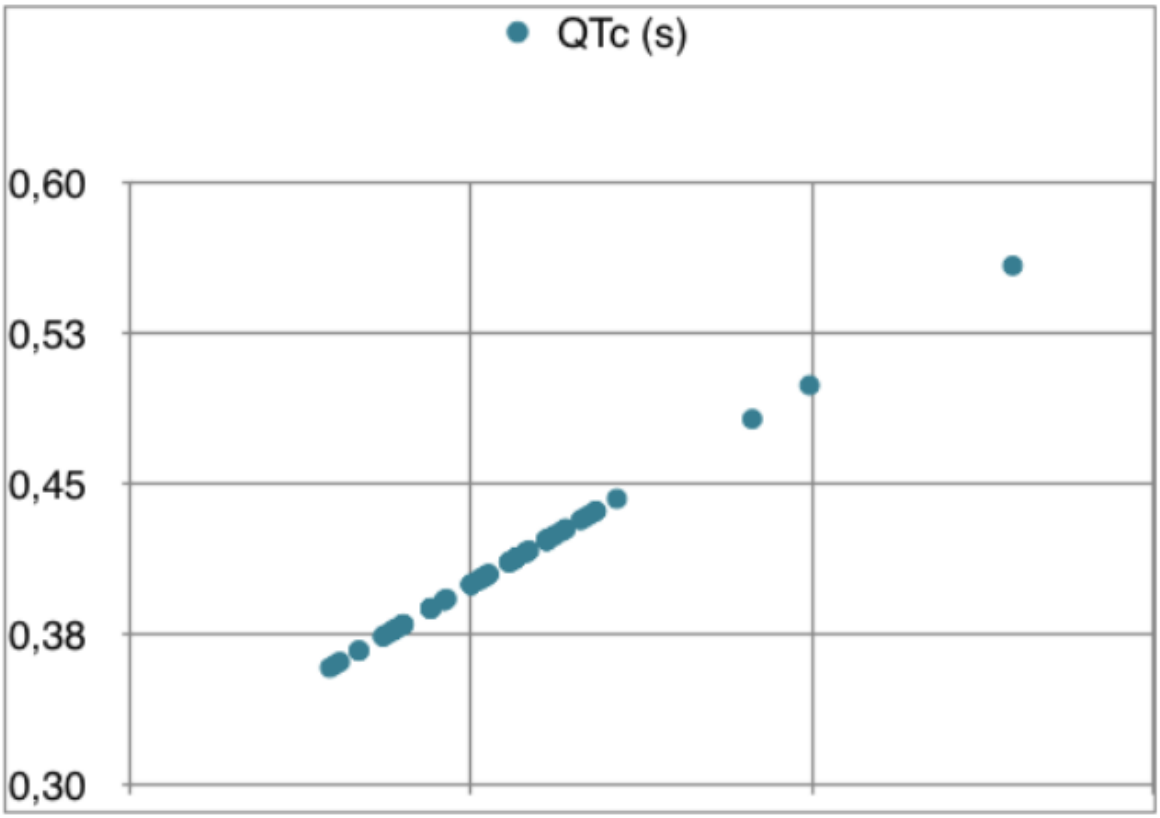
Mean QRS/T wave frontal angle (°)	QRS/T wave angle ≥60° (n, %)	QRS/T wave angle <60° (n, %)
18.42±26.23	(10, 13.3)	(62, 82.7)

Table 13. QRS/T wave frontal angle within the cohort. Of the patients studied, 13.3% had a angle ≥60° (probably pathological); of them, 5.3% (n=4) presented with an angle ≥90°C. No relationship with fever was observed. Of note, the SD is higher than the mean value, reflecting great dispersion of the value within the study population.

3. QTc interval Mean QTc interval in our study population was 408±31 msec (min 359; max 559 msec).

In three cases QTc resulted to be ≥450 msec. To all of them, follow-up was assured.

Results are depicted in Graph 2.

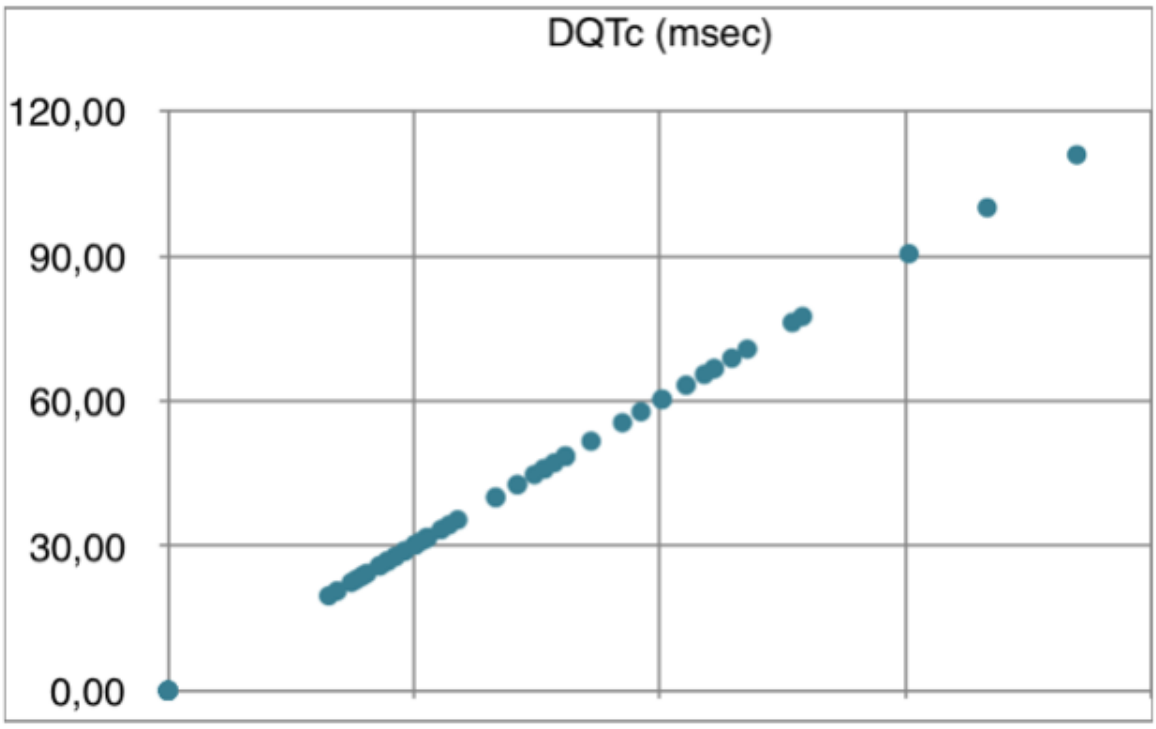


Graph 2. QTc distribution in the study population

4. QT dispersion and QTc dispersion. QT dispersion and QT dispersion were both calculated. Mean QT dispersion was 26.67±18.40 msec, while mean QTc dispersion was 35.64±24.91 msec (median 31.62 msec, max 110.94, min 0.00). Graph 3 and Table 14 illustrate the results.

We compared children with personal or familial history of seizures or arrhythmias, seizures vs. syncope, febriles seizures vs. nonfebrile seizures, fever vs. no fever in order to find out if QT dispersion was different between subgroups. Subgroups identified according to the presence or absence of fever and according to presence or absence of familial history were also compared in order to identify differences as far as the QTc dispersion is concerned. The distribution of values was approximately normal for each group. Statistic calculations were carried out by means of a Mann-Whitney U-Test considering a p value threshold of 0.005 as statistically significant. Results are summarized in Table 15 and Table 16. Although no statistically significant result was found, the majority of patients with a QTc dispersion ≥60 sec was represented by patients attended to for febrile seizures (see Graph 4). The small number constituting each subgroup may explain the absence of statistically significant results.

Finally, the main clinically characteristics of patients with increased QT and QTc dispersion are summarized in Table 17.



Graph 3. DQTc distribution in the study population

Mean QT dispersion (msec)	Mean QTc dispersion (msec)	Patients with a QTc dispersion ≥60 msec (n, %)
26.67±18.40	35.64±24.91	14, 18.6%

Table 14. Mean QT dispersion, mean QTc dispersion and number and relative percentage of patients in our cohort with QTc ≥60 msec (probably abnormal according to data from Literature).

Subgroups	Mann-Whitney U-test result
Febrile seizures vs. Nonfebrile seizures OR syncope	Z score 0.825 p value 0.412
Any seizure vs. syncope	Z Score -0.801 p value 0.424
Febrile seizures vs. Nonfebrile seizures.	Z Score -0.621 p value 0.535
Personal or familial history vs. children without	Z score -1.35 p value 0.17

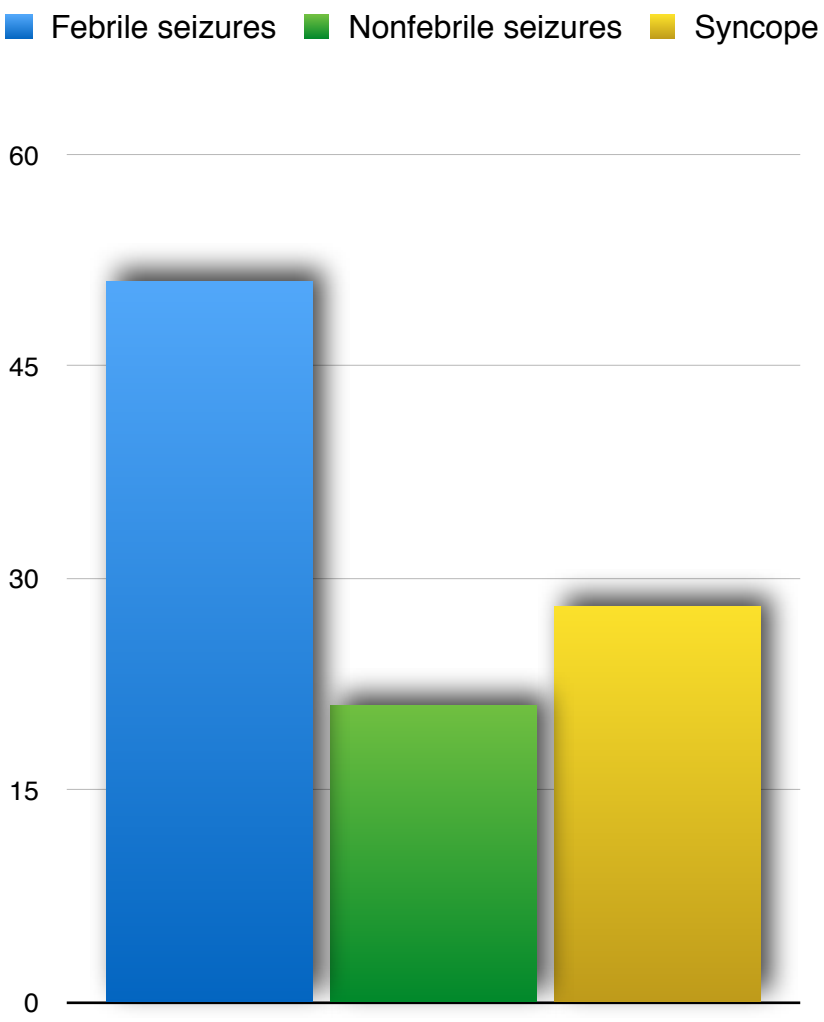
Table 15. Comparison of the mean QT dispersion between subgroups within our cohort. No statistically significant differences are found at p ≤0.05) using a Mann-Whitney U test.

Subgroups	Mann-Whitney U-test result
Febrile seizures vs. Nonfebrile seizures Or syncope.	Z score -0.4 p value 0.68
Personal or familial history vs. children without	Z score -1.6 p value 0.11

Table 16. Comparison of the mean QTc dispersion between subgroups within our cohort. No statistically significant difference was found at p ≤0.05 using a Mann-Whitney U test.

Number	QTc (msec)	QTd (msec)	QTc d (msec)	Diagnosis	Fragmented QRS (lead)
4	392	60	90.45	febrile seizure	V1, V2, aVL
7	379	40	63.25	febrile seizure	DIII, aVF
8	559	60	76.20	nonfebrile seizure	DIII, aVF, V2, V4
9	413	60	77.46	syncope	DIII, aVF, V1
22	393	60	65.47	syncope	no
26	400	60	100.00	febrile seizure	DIII, aVF, aVL
28	424	40	70.71	febrile seizure	DIII
34	400	40	66.67	febrile seizure	no
35	422	40	60.30	febrile seizure	aVL
42	422	40	60.30	nonfebrile seizure	DIII, aVL
45	422	40	60.30	nonfebrile seizure	no
49	400	40	66.67	febrile seizure	no
70	416	80	110.94	syncope (during sport)	DIII, aVF, V1
72	413	60	68.82	syncope	aVL

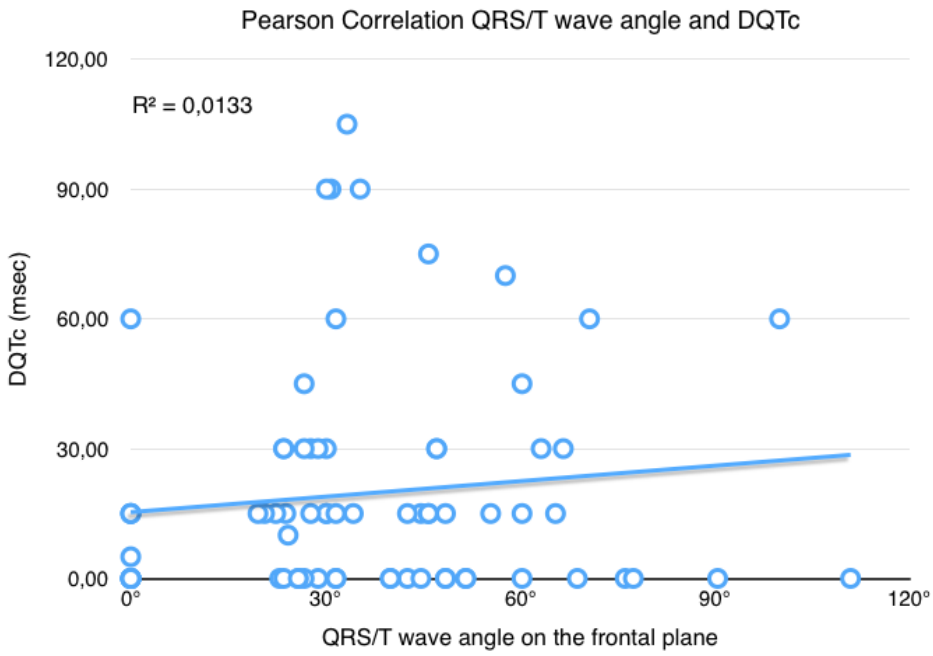
Table 17. Clinical and ECG Characteristics of the 14 patients with increased QT dispersion and QTc dispersion.



Graph 4. 50% of patients with QTc dispersion ≥60 msec had a first or a previous febrile seizure.

5. The relationship between QTc dispersion and the QRS/T wave frontal angle was studied calculating the Pearson correlation coefficient.

A statistically significant, although weak, positive correlation was found ($r=0.123$, $r^2=0.0152$), as illustrated in Graph 5.



Graph 5. Pearson correlation test between QRS/T wave frontal angle and QTc dispersion. A positive, statistically significant correlation was found.

Although no statistically significant difference was found between mean QTc dispersion between the febrile seizure and the nonfebrile seizure or syncope groups, it is true that among those patients that presented a probably pathologically high QTc dispersion (≥60 msec), the majority had either an actual febrile seizure or a had a history of febrile seizures, as previously commented (see Graph 4). Furthermore, these same patients had in the majority of cases a fragmented QRS in two leads, probably contributing to the QTc dispersion itself (n=8, 57%).

Chapter 5.

Discussion

The present study analyzes the ECG characteristics of a pediatric population attended to in an Emergency Department for an episode of loss of consciousness due to either a syncope or a seizure.

It is an observational study and the first one with such a purpose.

The most important aspect to underline is that a completely normal ECG was present in less than 50% of patients.

The abnormalities that were detected were considered important enough as to repeat an ECG and/or to discard a cardiac disease in 12 patients with high priority (19% of the total - and more of our cohort are to be evaluated) and subsequent follow-up was needed in 7 of them as of today; in particular, the study allowed for detection of two possible cases of cardiac pathology, although the results of the follow-up study are not part of this thesis. This means that realizing an ECG as a part of the initial study of the pediatric syncope and seizures may change the clinical attitude towards pediatric patients presenting for either seizures or syncope at the Emergency Department.

Let us examine the ECG characteristics of the populations in order to drawn further, more detailed conclusions.

Rhythm. in our population no clinically significant rhythm disturbances were detected. This may be due to the fact that the number of patients was not high enough, or that the monitorization was not prolonged enough during the patients' stay in the ED. Another possibility is that the patients with arrhythmias presenting with higher clinical instability were not included in the study.

One patient presented with a low-left (or coronary-sinus) atrial rhythm, and had been attended to for syncope. Given the reason for which she had come to medical attention, a 24-hour ECG Holter was performed, in which she alternated sinus rhythm and left atrial rhythm in the absence of any other abnormality. Two other patients attended to for syncope in one case and for febrile seizure in the other case presented with a high left atrial rhythm.

QRS abnormalities.

a) QRS Voltages Literature has demonstrated that the analysis of voltages per se yields poor results as far their predictive value of ventricular hypertrophy is concerned. For this reason, we decided to calculate the Soklow and Cornell indexes in each ECG of our study population, which resulted to be altered in each in 7 patients. Some of these patients have already been offered clinical follow-up. None of those who have accepted and have been studied by means of an

echocardiogram resulted to have a significant ventricular hypertrophy up to now. Interestingly enough, the pediatric hypertrophy index resulted to significantly reduce the number of patients with an ECG-defined LV hypertrophy.

At this point, two considerations are worth making. First, cardiologists normally advocate for the inclusion of other ECG data in order to express themselves as to the probability that the patient has a left ventricular hypertrophy. The voltages of the QRS complexes are just a part of the probability index that should be calculated, the other ones being the presence or absence of the instrinsecoid deflection, the presence or absence of abnormalities of the repolarization and morphologic abnormalities of the P-wave suggestive of a left-atrial enlargement and a leftward QRS axis deviation.

Both the Sokolow and the Cornell index have poorly performed as electrocardiographic predictors of LV hypertrophy. On the other hand, the pediatric hypertrophy index has been validated in patients with hypertrophic cardiomyopathy. This index has demonstrated a very high specificity and sensitivity even in those patients that were only genotype positive.

Which are the implications in a non-selected population as our study population? Following a prudential approach, the patients with a pathologic pediatric hypertrophy index (>23) even in the case of an initial normal echocardiogram should be probably granted a cardiological follow-up. In the absence of a pathological, echocardiographically - demonstrable hypertrophy in the moment of the immediate evaluation after the episode of loss of consciousness, the attitude to follow and the significance of the ECG index is less clear. It is the investigator's opinion that these patients, more than the patients' with a Sokolow or a Cornell index, should be at least carefully followed-up.

b) QRS fragmentation Another interesting data was the presence of a fragmented QRS in quite a large number of the patients we studied. This feature of the ECG has been widely studied in the adult population and is sometimes observed in children as well, especially if the child has an known cardiac disease or has been previously submitted to a cardiac surgery. However, the meaning of a fragmented QRS in the ECG of an otherwise healthy child has never been studied.

The definition itself of fragmented QRS in this population should be probably reformulated: in the adult population, in order to define the QRS as "fragmented" it is necessary to see at least two contiguous QRS

complexes having an additional R wave (R') or additional notching in the nadir of the notching in the nadir of the S wave, or the presence of >1 R' in two contiguous leads, corresponding to a major coronary artery territory. However, in the case of a child, in whom the leads cover a much larger area due to the size of the heart relative to the size of the leads themselves, doubts as far the requirement of the two contiguous leads could be raised.

In our study population, we found thirty-three patients with at least one lead presenting a fragmented QRS, seventeen of whom strictly met the definition thought for the adult population.

The striking characteristic of our population is the high prevalence of children with at least one lead in which the QRS complex looks fragmented. Unfortunately, there are no data as to the prevalence of such an ECG characteristic in healthy children. The prevalence of fragmented QRS, taking into account those patients in which there is just one lead meeting the definition, is as high as 44%.

Fragmentation is often associated to her ECG abnormalities. 13 children presented a fragmented QRS in anterior leads among others, and 22 presented fragmentation in at least one lateral lead. This makes an important difference in comparison with the general healthy adult

population, in whom fragmentation in anterior and lateral leads is relatively rare [59].

We also tried to analyze if having either personal or a familial history of arrhythmias, epilepsia, or seizures was more likely to be associated to the presence of a fragmented QRS within our study population. The results seem to go in favor of this hypothesis, being the prevalence of a fragmented QRS more frequent on the surface ECG of those patients with a personal or familial history of seizures, epilepsy or arrhythmias, even though the results are not statistically significant. Nonetheless, the small size of our study population, the heterogeneity of the conditions that were comprised under the name "seizure", "epilepsy" and "arrhythmias" (which in many cases could no be detailed) actually underline the need for further studies on this subject before any conclusion can be drawn.

Interestingly enough, a difference in the prevalence of fragmented QRS was noted when comparing children presenting with a febrile seizure or with a history of febrile seizures versus those attended to for a nonfebrile seizure or that had never had a febrile seizure. This would imply that QRS fragmentation is more frequent in those individuals that present a tendency to have seizures with higher body temperatures, and would probably suggest that a part of these children do have

different electrophysiological characteristics. From a clinical perspective, it would probably be interesting to follow up these individuals among others, though we still lack the information that a prospective study would grant us.

In the “Introduction” section we presented the physiology of the ion channels that are located in the heart and in the brain and we commented on the tight relation that exists between the ion channels and the structural proteins in the cardiomyocytes. We briefly mentioned the fact that the structure of the desmosome depends on the integrity of the sodium channels as well as on the correct functioning of other proteins such as Cx43, that change their location within the cell throughout the first years of one person’s life.

On the other hand, a growing body of literature has pointed out that the distortion of this fine architectural organization plays an important role in some channelopathies like Brugada syndrome. We speculated that a part of the reason why channelopathies are difficult to diagnose in childhood might depend on the fact that they are evolutive diseases, in the sense that the distortion of the architectural organization on the cell that they determine needs time to become clinically relevant.

For the same reason, the ECG signs that we need to look for might not always be same at every age in every individual, or, more simply, there may be a clinical spectrum of disease to which various conditions (febrile seizures and altered ECG, i.e. fragmentation of the QRS in one individual, Brugada syndrome in another individual) belong. This idea needs further confirmation through prospective studies on this population, i.e. children presenting with febrile seizures and an altered ECG.

Our study is an observational one, that may have simply identified a subpopulation of children among the many attended to for a quite common condition that deserve a different kind of medical attention both at the moment of the acute acute episode and in the future. Up to now, seizures in children have been regarded upon as neurological conditions, either primary or secondary, and benign in most cases. We do not mean to disagree with this statement, but to introduce some nuances in order to better our knowledge of channelopathies in children.

What is clear is that fragmentation of the QRS complex is a phenomenon still under study, mostly ignored in the pediatric ECG, even though many Authors have related it to an increased risk for sudden cardiac death in the adult population. Its meaning in the context

of an episode of loss of consciousness of uncertain significance should be further detailed, especially in pediatric patients.

Repolarization. As to the repolarization phase, the majority of patients with altered repolarization that have repeated an ECG up to now, did normalize it. The alterations we appreciated were in the majority of cases not suggestive of any diagnosis per se, and were more frequently seen in those children attended to for a febrile seizure and of minor entity.

a) *General alterations of the repolarization phase.* ST segment deviation, T-wave inversion or complete flattening of T waves were considered pathological and patients presenting such findings were invited to repeat the ECG tracing after the acute episode. The absence of normalization was considered suggestive of an underlying cardiomyopathy unless otherwise proven, although not necessarily related to the seizure or syncopal event for which the patient had been attended to in the ED. In 5 cases the alterations of the repolarization phase were pathological enough to indicate follow-up per se. Details of the ECGs of some of these patients are shown in Figure 13. We do not have obviously any possible comparison with the general population, as abnormalities of the repolarization phase are obviously not considered part of a normal ECG. It is worth

mentioning a paper by Miga et al. [60] who studied the prevalence of repolarization abnormalities (in detail, QTc and JTc prolongation as well as abnormalities of the T-wave vector) in children with structural normal hearts and premature ventricular contractions (PVCs), finding out a statistically significant higher prevalence of QTc and JTc prolongation (but no abnormalities as far as the T-wave axis was concerned) when compared to children without PVCs. In our subgroup of patients, two children presented with a prolonged QTc and a generally pathological repolarization phase, but the rest of them had a normal QTc. Literature has studied the phenomenon of the changes of cardiac repolarization in the context of seizures as well. Studies carried out on adult patients have brought to light the relative frequency of alterations in the ECG tracings of epileptic patients, relating it to cases of myocardial ischemia and/or arrhythmias and potentially to cases of SUDEP (sudden unexpected death in epilepsy) [61]. Cases of cardiac injury in prolonged seizures have been described [62], and in such patients repolarization abnormalities are common, as well as elevation of troponins.

Within our cohort of patients we should probably distinguish between those who present a seizure with a non diagnostic pattern of altered repolarization that reverts to normal when a new ECG tracing is obtained (such cases 31 or 44) from those patents in whom the alterations are associated with a prolonged QTc and deserve further

study to discard a LQTS (cases 8, 36, 66), and cases in which the altered depolarization per se are particularly marked, do not revert or are associated to a clinical history that would suggest the presence of an underlying cardiomyopathy until proven otherwise (cases 8, 36, 66, 31 among others).

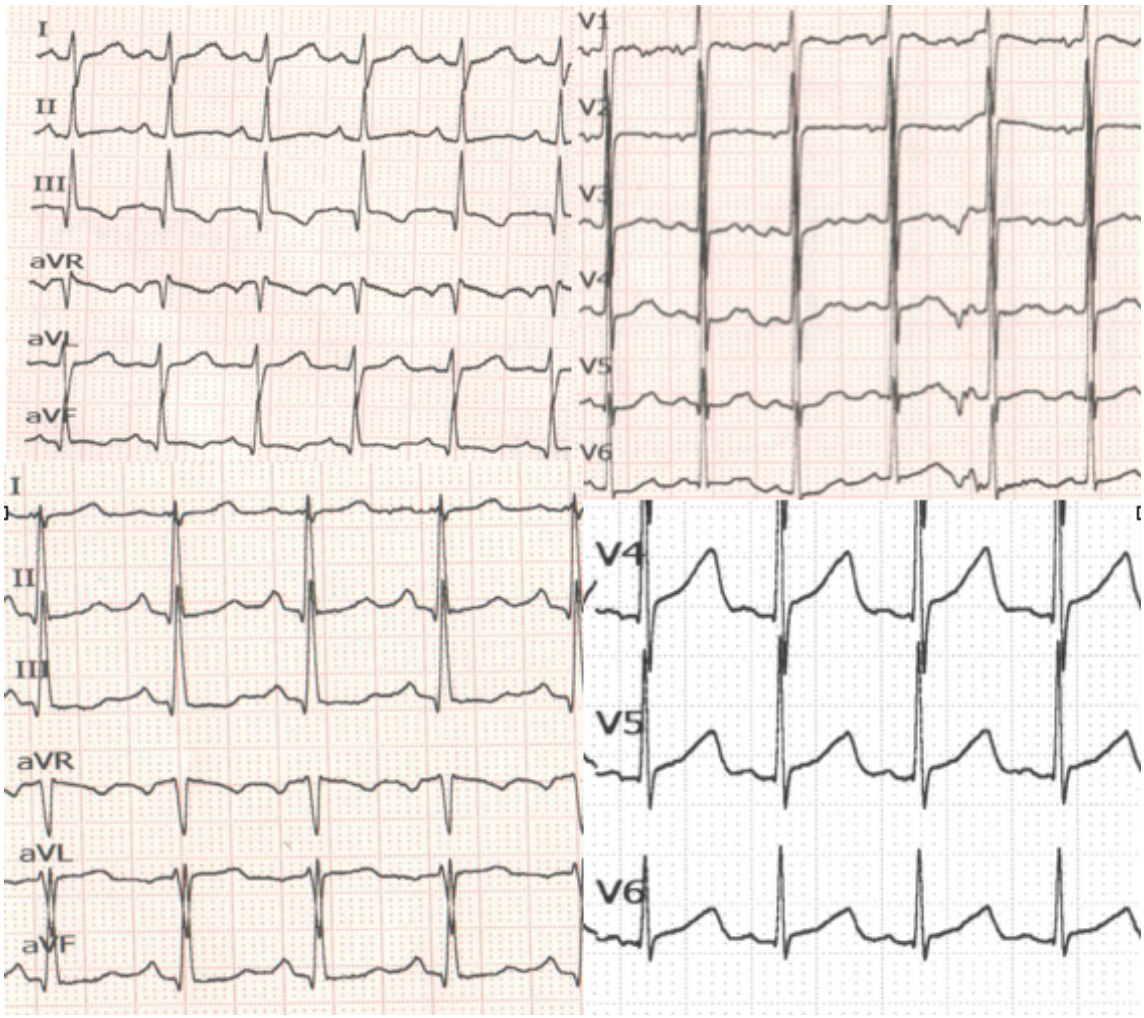


Figure 13. Details of the alterations of the repolarization of four patients. Above, left, patient 64 (1.29 years, febrile seizure), flattening and inversion of the T wave on the inferior leads. Above, right, patient 31 (nonfebrile seizure, 2.36 years; flattening of T wave (V1, V2 lead), slight depression of the ST segment (V3-V6). Echocardiogram and repeated ECG were normal. Bottom, left, patient 66, febrile syncope, 13.59 years, flattening of the T wave and slight depression of the ST segment (inferior leads). QTc 480 msec. Normal echocardiogram but persistent alterations on a new ECG. Stress test pending. Bottom, right, patient 6, nonfebrile seizure, 0.36 years, elevation of the ST segment between V4-V6. New ECG was normal.

b) *QRS/T wave frontal angle.* Interestingly, the ten patients who presented a QRS/T wave angle on the frontal plane pathological for being ≥60° did have the most significantly altered repolarization, not only because of the inversion of the T wave that conditioned the result of the angle on the frontal plane, but because they were also those that had the most significant alterations of the ST segment (not considering early repolarization). QRS/T wave angle is a very easy tool to use in whichever clinical setting. We chose the frontal plane in order to be able to calculate it without the need for any machine to be involved in the study. It is also a good way to formally summarize the alterations of the repolarization phase. To sum up, the presence of an altered QRS/T wave angle deserves attention, as the patient may need to repeat the ECG and probably further follow-up.

c) *Early repolarization.* Early repolarization could be observed both in children who presented at the ED for syncope or nonfebrile seizures, with a neat prevalence in those who had had a syncopal episode. As expected, no sign of early repolarization was found in the ECGs of those patients attended to for febrile seizures, as these patients are normally younger (otherwise the febrile seizures would be atypical). Of those that had been diagnosed with syncope, only 42% meet the criteria for early repolarization and half of them had had a previous

syncopal episode. Early repolarization is an argument of debate in literature as far as its prognostic implications are concerned, although it has been classically regarded upon as a benign finding that would support the diagnosis of a syncopal episode of vagal origin. The implications of early repolarization on the ECG tracing of the patients who presented at the ER for a nonfebrile seizure are less clear (Figure 14). These patients are older than the average cohort attended to for seizures (3871.6 days - 10.6 years - vs. 1543.2 days - 4.2 years, which was the mean age of children attended for any type of seizure). On the other hand, the mean age of children attended to for syncope was 3579.18 days - 9.8 years.

Why is early repolarization found in the ECG of these children? It may depend on a vagal activation starting after the seizure itself, although the mean cardiac frequency in these patients (who are just five, obviously too few to drawn any statistical conclusion) was 93.25 bpm (min 54, max 118 bpm), being in just one case clearly associated to bradycardia (54 pm). One should not forget that the ER pattern has already been found in epileptic patients. In 2014, for instance, Lamberts and colleagues [63] compared the ECG of 185 patients with drug-refractory epilepsy (mean age 38 years), and compared them with the tracings obtained from 178 controls with no history of either epilepsy nor psychiatric disorder. Among others, there was a

statistically significant difference in the prevalence of ER pattern, being this more commonly found in epileptic patients. The Authors corrected the result for the "epilepsy" variable in a multivariate analysis, and the result remained statistically significant, suggesting a direct relationship between epilepsy and the phenomenon of ER. The hypotheses at the basis of such a finding may be essentially two: either an abnormality in the autonomic balance induced by epilepsy, as the Authors of the paper themselves suggest, or an abnormality in the ionic currents that would exist in the patient both at neuronal and cardiac level. Early repolarization can be explained as the result of an imbalance between the repolarization currents and the depolarizing currents generating the action potential. It is a fact that an ER syndrome has been identified as the product of a mutation of the KCNJ8 gene and of the CACNA1C and CACNB2B genes, which are implicated in the regeneration of the inwardly-rectifying potassium current and of the calcium current.

That epilepsy and ER might be somehow related seems to be further confirmed by another - very recent - study, in which Chyou et al [64] found out that epileptic patients that had suddenly died compared to living epileptic patients had both a higher prevalence of ER in their ECG tracings compared to the general population, although the two

groups they compared to each other did not present a statistically significant difference.

Three of the patients in our cohort presenting for a nonfebrile seizure with ER pattern on their ECG were returning to the ED for a new seizure, whereas the other two children were experiencing their first seizure.

Further studies may be probably able to clarify the role played by ER in pediatric patients with nonfebrile seizures, and if this ECG finding changes their prognosis or not.

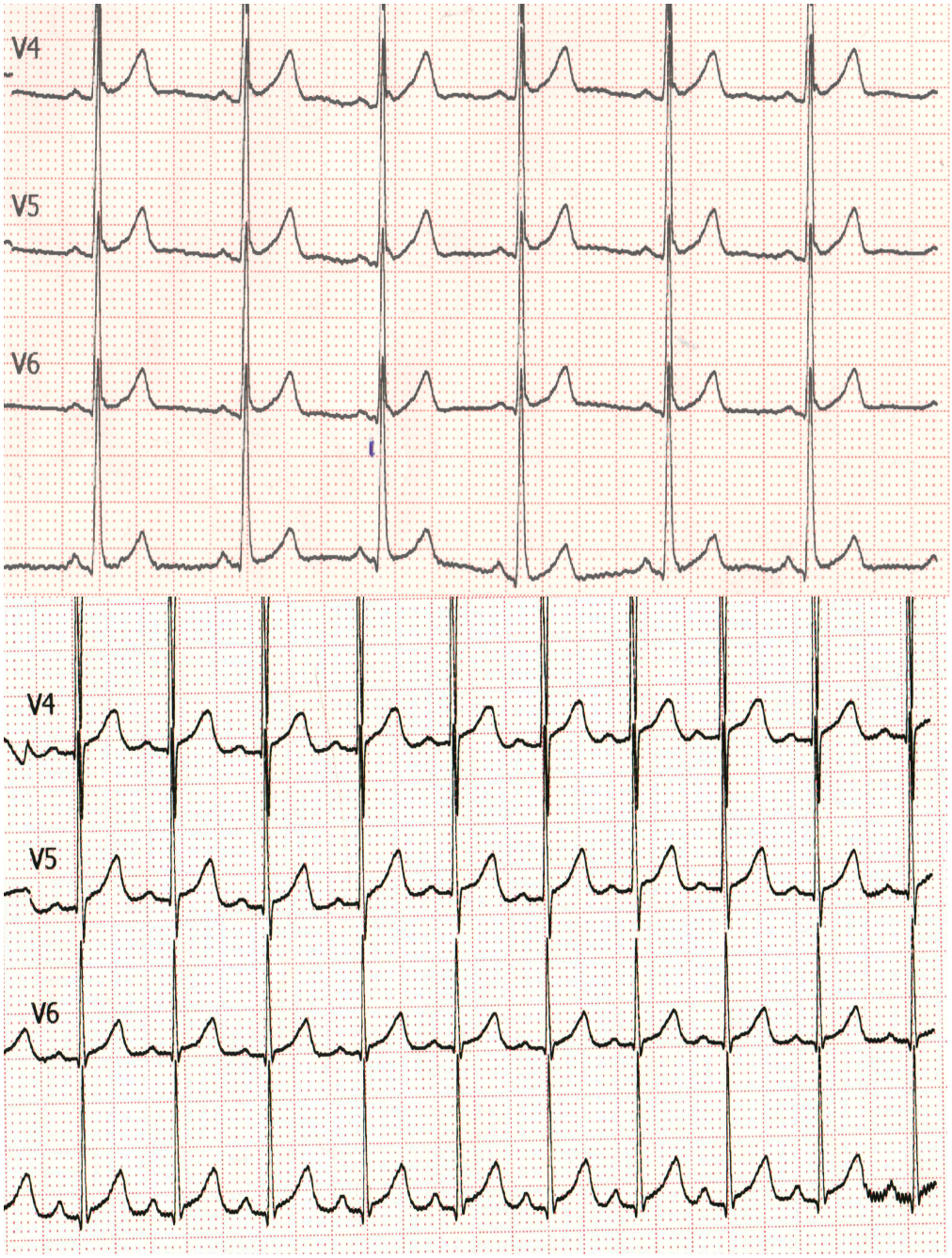


Figure 14. Details of the ECG of two patients presenting with nonfebrile seizures. Early repolarization was observed in their tracing. Above, patient's 69 ECG. Age at the moment of the episode was 14.33 years. Bottom: patient's 14 ECG, age at the moment of the episode was 1.42 years.

d) QTc. One of the main goals of analyzing a pediatric patient's ECG in the ED is the analysis of the QTc.

We previously commented on the difficulties that this task implies, and on the fact the a single measure does not allow to rule LQTS out if a reasonable clinical picture exists.

The relationship between LQTS and epilepsy is quite strong, and pediatricians should be aware of that.

In our cohort we found one patient with a clearly pathologically long QTc that had been attended to for a nonfebrile seizure at age 12.6 years. She had already had nonfebrile seizures but no cardiological study and been previously performed. Her ECG is shown in Figure 12.

A second patient, aged 12.4 years, with a history of febrile and nonfebrile seizures, presented with a prolonged QTc and marked altered repolarization (Figure 11).

Finally, a third patient presented with a QTc measuring 480 msec in the context of a marked altered repolarization (Figure 15). She had been attended for a febrile syncope and had no previous personal or family history suggestive of cardiac diseases.

In all cases, follow-up and further study were assured.

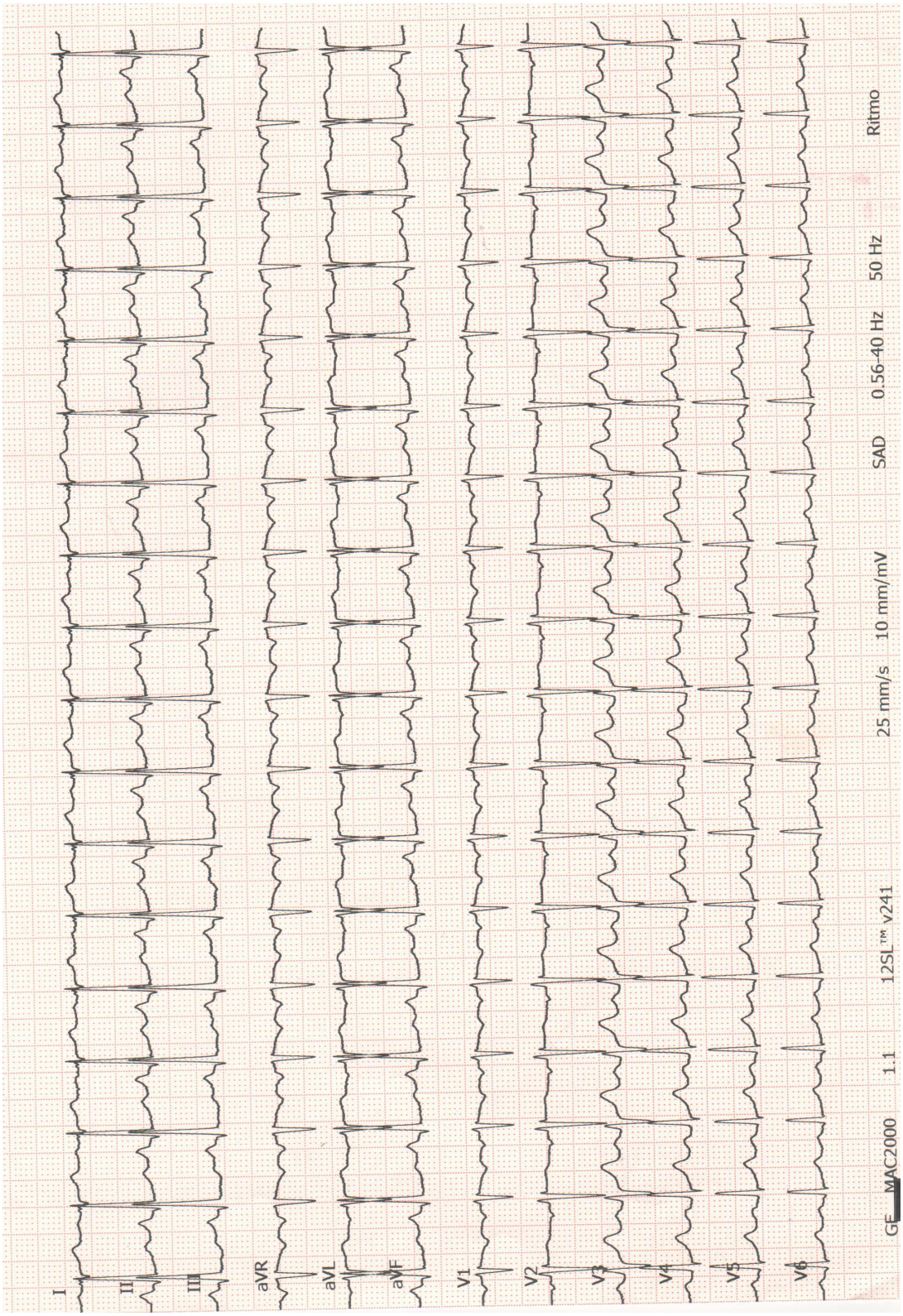


Figure 15. The ECG of one of the patients attended to for a febrile syncope. Note the prolonged QTc in the context of an abnormal repolarization phase. Subsequently repeated ECG demonstrated persistence of the abnormalities, but the echocardiogram was normal. Follow-up is ongoing.

What do these data suggest? In our cohort, we found 3/75 (4%) patients with abnormally long QTc.

In two cases, the patient had been diagnosed with a seizure, and it was not the first episode that she/he had presented.

The importance of the diagnosis may per se justify the use of the ECG as a diagnostic tool in patients attended to for seizures.

In literature there are several studies that have described the association between LQTS and epilepsy, or better, with seizures.

Case reports, such the one described by Omichi et al [65], describe examples of coexistence of epilepsy and LQTS in the same individual, with LQTS being a late diagnosis. We have already mentioned that mutations in the potassium channels may be responsible for arrhythmogenic diseases and epilepsy at the same time, and the well-known Andersen-Tawil, Jervell-Lange-Nielson syndromes are both variants of LQTS involving the central nervous system as part of their spectrum of disease.

In an interest study in vitro, Burashnikov [66] demonstrated that in the context of LQTS, an increase of temperature may trigger arrhythmias. The Authors examined cells obtained from the left ventricle (both M cells and Purkinje cells), recording both the cellular

action potential and a simultaneous transmural ECG. Hyperthermia accentuated transmural dispersion of action potential duration and facilitated early after depolarizations, facilitation the development of torsade de pointes. LQTS electrophysiological conditions were reproduced dissolving a highly selective I_{Kr} blocker, E-4031 and a relatively specific I_{Ks} blocker.

The clinical implications as far as a population of children attended to for febrile seizures are quite straightforward: an ECG should be obtained and interpreted in these patients as well, as patients with LQTS may have a higher tendency to develop arrhythmias in the presence of fever.

e) *QT dispersion and QTc dispersion*. In our population mean QT dispersion was 26.67±18.40 sec, while mean QTc dispersion was 35.64±24.91 msec.

There has been a great dispute in literature over the opportunity to correct QT dispersion for heart rate or not, and no real conclusion seems to have been reached [67]. In any case, our mean values fall within normal limits.

The meaning of QT dispersion has been a matter of debate as well [68].

For quite a long time, the cardiological community has insisted on considering it an electrocardiographic parameter reflecting the inhomogeneous repolarization state characterizing certain heart diseases and as such, it would serve as a marker of arrhythmogenic risk. This hypothesis has been refuted using the arguments of vector electrocardiography: QT dispersion cannot reflect different repolarization times in different areas of the myocardium because the repolarization time is only one, and the electrode recording the end of the T-wave at a given time is simply doing so because at that moment the difference of voltage between that electrode and any another point must be zero. In other words, the end of T-wave in any given lead is a projection onto that lead of the T-loop, namely the repolarization vector generated by the whole heart after the depolarization phase. As such, QT dispersion is a gross reflection of any abnormality of the T-loop morphology (of its initial and terminal axis, its amplitude, duration and width), and is not able to reflect patchy repolarization properties within the myocardium. Still, it surely retains a prognostic value.

The largest studies on the subject defined normal QT dispersion ≤50 msec (including children and neonates) [69] and normal QTc dispersion <40 msec [70] (even though the mentioned study did not include children); furthermore, the Rotterdam study specified that the

increase in the risk of sudden cardiac death clearly appeared related to a QTc >60 msec. In an other study, Tutar et al. [71] examined a cohort of healthy children and fund out a mean QTc of 47.9±16.9 msec for boys and of 46.5±16.2 msec for girls (29.9±10.2 msec for the whole group), with the 95th centile at 80 msec as for boys and at 75 msec as for girls.

Therefore, even with great overlaps, it seems that QTc values ≥60 msec are at least unusual if not associated with an arrhythmic risk, and that values ≥90 msec are even more clearly above the the limits reported by the majority of studies.

We decided to evaluate the correlation between QTc dispersion and QRS/T wave frontal angle, another parameter summarizing the alteration of repolarization in our cohort, finding out a positive (although weak) correlation. This result is logic according to the interpretation of QTc dispersion as another parameter of altered repolarization. The wider the QRS/T wave angle, the more altered the repolarization; the longer the QTc dispersion, the more altered the T-loop.

The correlation is weak probably due to the fact on one hand that the measurements were done manually, limiting their resolution, and on

the other hand, that we correlated the value of the QRS/T wave angle on the frontal plane, which is an expression on one plane of the QRS- and T-wave loops, while QTc dispersion, as previously commented, would be rather the result of the spatial T-loop morphology.

We should then examine those patients within our cohort with the highest QT and QTc dispersion.

Seven patients presented with a QT dispersion value ≥60 msec and fourteen with a QTc value ≥60 msec, of whom three had both a QT dispersion value ≥60 msec and a QTc value ≥90 msec, great enough not to represent a simple measurement mistake (see Table 17).

50% of the patients with high QT dispersion and QTc dispersion had been attended to for a febrile seizure. One patient had been attended to for a syncope that had occurred during effort, one other had recurrent syncopal episodes with fever and a previous history of atypical febrile seizures (the last one occurring indeed at 7 years of age). Eight patients with high QTc dispersion values had fragmented QRS complexes in two leads as well, which we previously discussed as a marker of inhomogeneous depolarization that has been linked to arrhythmic risk per se. Within the group of patients with fragmented QRS, those with prolonged QTc dispersion represented only a small minority (8 out of 32 had both ECG features).

The connection between these two electrocardiographic elements is not clear. With just a surface ECG and 75 patients, we can only speculate. One would argue that fragmentation may increase QTc dispersion, interfering with QT measuring in a given lead, although not all the patients with fragmented QRS have an increased QTc dispersion value. Probably, it is an association highlighting the depolarization inhomogeneity that characterizes the myocardium of these subjects on one hand and its altered repolarization vector on the other hand, being the latter the result (or not) of the first one.

What seems to be clear is that performing an ECG in pediatric patients attended to for a loss of consciousness reveals the presence in some of them of unexpected markers of arrhythmogenic risk that would deserve further study.

Automated interpretation of the ECG vs. manual interpretation.

The ability to interpret correctly the pediatric ECG by physicians in the Emergency Department was tested in a study realized in 2003 by Snyder and colleagues [72]. When compared with electrophysiologists', Pediatric Emergency Department Physicians' performance resulted especially poor at evaluating the most important ECG diagnoses, such

as prolonged QT intervals (0% of them ascertained), ST abnormalities and early repolarization (10% evaluated them correctly).

Automated interpretation of the ECG is not a good tool either. In the same study, the computer resulted a valuable tool to evaluate atrial enlargement and ventricular hypertrophy but its performance in diagnosing repolarization abnormalities proved especially poor, with none of the prolonged QT intervals and no case of ischemia correctly picked-up.

For this reason, each ECG in our study was first evaluated by one of the physicians of the Emergency Department (who was in charge of the patient in the immediate moments following the acute episode and who was, most often, but not always, a pediatric resident) and subsequently, revised by two cardiologists (the investigators involved in the study).

Although not one of the aims of our study, we could see that a careful review of the tracings by an experienced observer proved useful to re-consider the original diagnosis in a variety of cases, among whom patients 8, 36 and 66 (each of whom with a prolonged QT interval). Therefore, we believe that the evaluation of the ECG of children attended to after an episode of loss of consciousness by an experienced cardiologist is highly recommendable.

PART 3.

Chapter 6.

Summary.

Conclusions and clinical perspectives.

The majority of children attended to for a febrile, nonfebrile seizure or syncope in the Emergency Department present at least minor abnormalities in the ECG tracing realized after the acute episode.

Although any type of abnormality might potentially be encountered, the most frequent ones are the alterations of the repolarization phase, which are an heterogeneous group of ECG findings: in our study, 17 patients presented an abnormal repolarization phase requiring a second ECG to better evaluate its clinical meaning, in five cases justifying follow-up on its own. In those in whom persistence of the alterations was observed, further investigations were deemed necessary. The lack of previous studies on this same subject has obliged the investigators to use a personalized approach for each patient.

It is clear from the data we obtained from our study population that children with syncope, febrile seizures and nonfebrile seizures are, quite unexpectedly, at least from an electrocardiographic standpoint, a very heterogenous group.

Within this group, it would be clinically important to recognize those patients that present any ECG marker of higher risk. These patients would need therefore either a cardiological evaluation during their stance in the Emergency Department, a longer observation time, or further follow-up.

There are some obvious, already-known indications to the previously commented measures, such as arrhythmias, pre-excitation, or evidence

of atrioventricular blocks; rarer in the pediatric population, but important to recognize, is the ECG evidence of myocardial ischemia.

However, in our study we concentrated on the less known, more pediatric-specific ECG findings of the repolarization phase that should prompt further clinical studies:

a) Prolonged QTc or increased QT dispersion (if calculated);
b) A QRS/T wave angle >60° (especially if ≥90°) or the deviation of the ST segment: either of which should be further evaluated to rule out an underlying cardiomyopathy or a channelopathy;
c) Persistence of negative T wave in the right precordial leads after 12 years of age or elevation of the ST segment in the right precordial leads;
d) Early repolarization in epileptic patients or patients with nonfebrile seizures.

As to the last point, based on what has already been described in the adult population, when early repolarization is observed in epileptic patients or children presenting for nonfebrile seizures, these patients may either require a longer and a thorougher period of in-hospital observation after the acute episode and/or further neurological and cardiological follow-up, although this is a point that in the pediatric population is still to be elucidated. Nonetheless, it is clear that early

repolarization could be observed in just a small proportion of our study population and its meaning ought to be the object of further clinical, prospective studies.

As to the depolarization phase, QRS morphology should be carefully examined to evaluate the probability of ventricular hypertrophy, which is theoretically higher in those cases in which high QRS voltages are associated with other ECG abnormalities (such as ST abnormalities, P-wave abnormalities, etc..) and in those cases in which more than one hypertrophy index turns out to be abnormal.

Based on the evidence provided by the literature on the subject, a prudential approach would be indeed to rule out ventricular hypertrophy in such cases in which more than one hypertrophy index is altered, especially if more than one ECG abnormality is encountered, or there is any positive family history, or if the reason for medical consultation has been an exercise-related syncope or the physical exam generated any suspicion.

In these cases, and in relation to the diagnosis of ventricular hypertrophy, a single echocardiogram might not be sufficient and a longer follow-up might be required. In our study population, nonetheless, none of the patients whose ECG tracing presented high QRS voltages has been diagnosed - as of today - with (left) ventricular hypertrophy but, if clinical history has raised any concern, follow-up has been assured according to the clinician’s criterion.

Another ECG characteristic that deserves to be recognized and should be the object of further studies is QRS fragmentation.

In our study population, 44% of children presented at least a fragmented QRS complex in their tracing, a proportion significantly higher in comparison to what is commonly reported in the healthy general adult population. Interestingly, children with febrile seizures presented fragmented QRS complexes more frequently than children without a fever. In our opinion, this is another matter of further research, since data on the prevalence and meaning of fragmentation of the QRS in the healthy general pediatric population are particularly scarce.

On a theoretical level, QRS fragmentation might serve as an indication of electrical instability and as of a marker of the presence of a potential channelopathy in that individual, the ECG expression of which might change over his or her lifetime or not. The biological bases of this assumption are the demonstration that the position and function of Cx43 and NaV1.5 change over infancy on one side, and the evidence that established channelopathies like Brugada syndrome determine structural changes on the other. These two data suggest that the functioning of ion channels and their mutations (channelopathies) possess to some extent an evolutive character. The expression at surface level (ECG tracing) might change as well. This does not mean necessarily that children with a fragmented QRS complex will be future

patients with a Brugada pattern or any other channelopathy. The clinical consequences of having a fragmented QRS complex since childhood (a higher incidence of epilepsy? A higher incidence of Brugada? A higher incidence of ventricular or supra ventricular arrhythmias? A higher incidence of ventricular dysfunction? No differences compared to the general population?) should be prospectively examined.

To summarize, as far as the alterations of the depolarization phase of the ECG are concerned:

a) QRS fragmentation;
b) Higher - than - normal per age QRS voltages when more than one hypertrophy index or other ECG parameters are altered

should prompt further clinical follow-up.

To sum up, our study highlights that the correct interpretation of the electrocardiographic abnormalities in a pediatric patient that is being attended to after a loss of consciousness requires an adequate knowledge of what the clinician may be confronted with, and the awareness that the ECG in a patient after a seizure or a syncope is a powerful instrument to detect potentially life-threatening diseases.

However, our study underlines that those alterations that do not yield a diagnosis per se, such as QRS fragmentation or the alterations of

the repolarization phase, represent an heterogenous group: each of them requires a separate process of reasoning on their meaning in a particular patient as well as on the opportunity to repeat the ECG after the acute phase and to provide a cardiological follow-up in the short as well as in the long-term.

Besides, our study points out that what has traditionally regarded upon as a benign condition, like febrile seizures, should also be considered as a potential opportunity to provide the patient with an important, life-saving, diagnosis on one hand, and, on the other hand, our work has allowed us to suggest certain important pathophysiological relationships between the cardiovascular and the nervous systems, which notoriously share some common molecular structures.

Moreover, conditions previously regarded upon as of exclusively neurological nature, such as nonfebrile seizures, can take advantage of the use of an ECG in order to stratify their own prognosis and to rule out associated cardiac channelopathies in the same patient.

Further studies will be able to elucidate how the ECG findings we highlighted in pediatric patients attended to for febrile, nonfebrile seizures and for syncope may possibly evolve in adulthood.

Capítulo 6. Resumen. Conclusiones y prospectivas clínicas.

La mayoría de los niños atendidos en Urgencias por convulsiones febriles, afebriles y por síncope presentan al menos unas alteraciones menores en el electrocardiograma realizado después del episodio agudo.

Aunque cualquier tipo de anomalía puede potencialmente encontrarse, las más frecuentemente evidenciadas fueron las alteraciones de la repolarización, un grupo heterogéneo de hallazgos electrocardiográficos: en nuestro estudio, 17 pacientes presentaban alteraciones de la repolarización, y cinco de ellos han tenido que volver a repetir un segundo ECG para confirmar la presencia de las mismas alteraciones. En aquellos pacientes en los que las alteraciones se han finalmente confirmado, se han solicitado ulteriores pruebas complementarias. La falta de estudios previos sobre el mismo tema nos ha obligado a enfocar de forma personalizada cada paciente en nuestro estudio.

A raíz de los datos obtenidos con nuestro trabajo, queda claro que la población de niños que son atendidos por síncope, convulsiones febriles y convulsiones afebriles es, bastante inesperadamente, un grupo muy heterogéneo desde un punto vista electrocardiográfico.
Dentro de este grupo sería especialmente importante reconocer aquellos pacientes que presenten algún marcador electrocardiográfico

de riesgo. Son de hecho estos pacientes que necesitarían una valoración cardiológica durante su permanencia en Urgencias, o un periodo de observación más largo, o un seguimiento tras el alta.

Existen algunos indicadores electrocardiográficos que obligan obviamente a las medidas previamente comentadas, como la evidencia de arritmias, de pre-excitación, o la evidencia de bloqueos aurículo-ventriculares y, más raramente en la población pediátrica, aunque importante de reconocer, los signos electrocardiográficos de isquemia miocárdica.

En nuestro estudio, nos enfocamos en aquellos hallazgos electrocardiográficos, relativos a la fase de repolarización, más típicos de la edad pediátrica pero también menos conocidos, que deberían generar ulteriores valoraciones:

a) prolongación del QTc o aumento de la dispersión del QT (si calculado);
b) un ángulo QRS/T (en en plano frontal) >60° (y especialmente si ≥90°) o una desviación del segmento ST deberían ser objeto de estudio para descartar la presencia de una cardiomiopatía subyacente o de una canalopatía;
c) Persistencia de una onda T negativa después de los 12 años de edad o ascenso del segmento ST en precordiales derechas;

d) Repolarización precoz en pacientes epilépticos o atendidos por convulsiones afebriles.

En relación al último punto, a raíz de lo que ya se ha estudiado en la población adulta, cuando un patrón de repolarización precoz se encuentra en pacientes epilépticos o niños que se presenten por convulsiones afebriles, esos pacientes pueden necesitar un periodo más largo o más intensivo de observación hospitalaria tras la propia convulsión, o un seguimiento neurológico o cardiológico, aunque es cierto que este punto todavía no ha sido estudiado de forma específica en la población pediátrica. De todas formas, queda claro que la repolarización precoz se ha observado en tan sólo una menoría de la nuestra población y su significado tendría que ser objeto de futuro estudios clínicos prospectivos.

En cuanto a la fase de despolarización, la morfología del complejo QRS debería evaluarse para valorar la probabilidad de hipertrofia ventricular, que es mayor en esos casos en los que voltajes elevados están asociados a otras anomalías del ECG (como anomalías del segmento ST y de la onda P…) y en aquellos casos en los que más de un índice de hipertrofia está alterado.

Un planteamiento prudencial y basado en las informaciones proporcionadas hasta ahora por la literatura sería intentar descartar la presencia de hipertrofia ventricular en aquellos casos en los que más de un índice de hipertrofia está alterado, en aquellos en que se ha

encontrado más de una alteración electrocardiográfica, en aquellos en que la exploración física genera dudas, especialmente si hay una historia familiar positiva de algún tipo, o si la razón de consulta ha sido un síncope con el esfuerzo. En todos estos casos, y en relación al diagnóstico de hipertrofia ventricular, un solo ecocardiograma, aislado, puede no ser suficiente, y un seguimiento en el tiempo podría resultar necesario. En nuestro estudio - hasta ahora - ninguno de los pacientes que presentaban tan solo voltajes elevados del complejo QRS ha sido diagnosticado de hipertrofia ventricular (izquierda), pero, en aquellos casos en los que la historia clínica haya generado preocupación, se ha garantizado seguimiento según el juicio del clínico responsable.

Otra característica electrocardiográfica que merece la pena reconocer y que debería ser objeto de ulteriores estudios es la fragmentación del complejo QRS. Al menos el 44% de los niños en nuestro estudio presentaba al menos un complejo QRS fragmentado en el ECG, un porcentaje significativamente más alto con respecto al que se describe en la población general adulta y sana. Resulta interesante observar que los niños con convulsión febril presentaban complejos QRS fragmentados más frecuentemente con respecto a los niños sin fiebre.
Es nuestra opinión que éste debería ser tema de investigación futura, ya que los datos acerca de la prevalencia y del significado de la fragmentación del complejo QRS en la población sana pediátrica son particularmente escasos.

A nivel teórico, la fragmentación del complejo QRS podría servir de indicador de inestabilidad eléctrica y de marcador de la presencia de una canalopatía potencial en un individuo, en el supuesto que la expresión clínica de la propia canalopatía podría cambiar a lo largo de la vida del mismo individuo. El fundamento biológico de esta suposición es la demostración de que la localización y el funcionamiento de la proteína Cx43 y del canal NaV1.5 se modifican a lo largo de la infancia por un lado, y, por el otro, la evidencia de que algunas canalopatías establecidas, como el síndrome de Brugada, pueden determinar la aparición de cambios estructurales. Estos dos datos sugieren que el funcionamiento de los canales iónicos y las enfermedades que de ellos dependen (las canalopatías), poseen en cierta medida un carácter evolutivo. Por lo tanto, la expresión a nivel de superficie (el trazado ECG), podría cambiar también. Esto no significa que los niños con complejo QRS fragmentado serán seguramente pacientes con síndrome de Brugada o con otras canalopatías.

Las consecuencias de presentar un complejo QRS fragmentado desde la infancia (¿Una incidencia más elevada de epilepsia? ¿Una incidencia más elevada de Brugada? ¿Una incidencia más elevada de arritmias? ¿Una incidencia más elevada de disfunción ventricular? ¿Ninguna diferencia con respecto a la población general?) deberían explorarse de forma prospectiva.

Para resumir, proponemos que:

a) La fragmentación del QRS;
b) Voltajes del complejos QRS más elevados para la edad, cuando más de índice de hipertrofia u otros parámetros están alterados

sean indicación de seguimiento clínico futuro.

En resumen, nuestro estudio evidencia que la interpretación correcta de las anomalías electrocardiográficas en el trazado de un paciente pediátrico atendido después de una pérdida de conocimiento requiere que el clínico sepa a que puede potencialmente enfrentarse, y que el ECG que se realiza tanto después de un síncope como después de una convulsión puede ser una herramienta extremadamente útil para detectar enfermedades potencialmente mortales.

Por otro lado, nuestro estudio subraya que existen alteraciones del ECG que no son diagnósticas de por si, como la fragmentación del QRS o las alteraciones de la repolarización, y que constituyen un grupo heterogéneo de anomalías: cada una de ellas requiere un proceso único de razonamiento acerca de su significado en un paciente concreto, así como sobre la oportunidad de repetir el ECG después del episodio agudo y de ofrecer un seguimiento tanto a corto como a largo plazo.

Nuestro estudio señala también que lo que tradicionalmente se ha considerado una condición fundamentalmente benigna, como las

convulsiones febriles, debería considerarse como una potencial oportunidad para ofrecerle al paciente, en unos casos, un diagnóstico importante y hasta salva-vida, y por otro lado, nuestro trabajo sugiere la existencia de ciertas importantes relaciones fisiopatológicas entre el aparato cardiovascular y el sistema nervioso, que notoriamente comparten algunas estructuras moleculares fundamentales para su funcionamiento.

Por otra parte, algunas condiciones que tradicionalmente se han considerado como de naturaleza exclusivamente neurológica, como las convulsiones no febriles, pueden sacar partido del realizar un ECG tanto para estratificar su propio pronóstico como para descartar la presencia de canalopatías cardíacas asociadas en el mismo paciente.

Estudios clínicos futuros podrán aclarar como los hallazgos electrocardiográficos que hemos descrito en los pacientes pediátricos atendidos por convulsiones febriles, no febriles y por síncope a lo largo de nuestro studio, podrían evolucionar durante la edad adulta.

SUMMARY OF CONCLUSIONS:

1. This is the first study to systematically analyze the ECG characteristics of children attended to for seizures or syncope in the Emergency Department (ED).
2. The majority of children attended present at least minor ECG abnormalities.
3. Our study population is - quite unexpectedly, at least from an electrocardiographic standpoint - an heterogenous group.
4. The absence of previous studies on the same subjects, especially in the pediatric population, makes it difficult to drawn conclusions on the meaning of each single observed abnormality.
5. As to the alterations of the depolarization phase: QRS fragmentation and higher-than-normal per age QRS voltages when more than one hypertrophy index or other ECG parameters are coincidentally altered should both prompt further follow up.
6. As to the abnormalities of the repolarization phase: a prolonged QTc or an increased QT/QTc dispersion (if calculated), a QRS/T-wave frontal angle >60° (especially ≥90°) or a deviation of the ST segment in more leads, a persistence of negative T waves in right precordial leads beyond 12 years, and the evidence of early repolarization pattern in patients with nonfebrile seizures should prompt further cardiac evaluation and/or follow-up.
7. The ECG might differentiate cardiovascular and neurological conditions, either co-existing or not.
8. The ECG might help stratify the prognosis of patients diagnosed with purely neurological conditions, though this should be further studied in pediatric patients.
9. At least some channelopathies (such as Brugada syndrome) might be regarded as evolutive diseases: in this regard, the way we look at the pediatric ECG should probably change. Further studies should focus on how the tracing of selected pediatric population of children might change in adulthood.

RESUMEN DE LAS CONCLUSIONES:

1. Éste es el primer estudio que analice de forma sistemática las características electrocardiográficas de los niños atendidos por convulsiones o síncope en Urgencias.
2. La mayoría de los niños atendidos presenta al menos unas anomalías menores en el ECG.
3. Nuestra población a estudio es - bastante inesperadamente, al menos desde el punto de vista electrocardiográfico - un grupo heterogéneo.
4. La ausencia de estudios previos sobre del mismo tema, especialmente en la población pediátrica, hace que sea difícil sacar conclusiones acerca de cada una de las anomalías encontradas.
5. En cuanto a las anomalías de la fase de despolarización: la fragmentación del QRS y los voltajes del QRS más elevados para la edad, especialmente cuando haya más de un índice de hipertrofia alterado o más de un índice electrocardiográfico anormal simultáneamente, deberían de constituir indicación a un seguimiento ulterior.
6. En cuanto a las anomalías de la fase de repolarización: un QTc prolongado o un aumento de la dispersión del QT o del QTC (si calculada), un ángulo entre QRS y onda T en el plano frontal >60° (especialmente si ≥90°), una desviación del segmento ST, la persistencia de ondas T negativas en las derivaciones precordiales derechas o la presencia de un patrón de repolarización precoz den pacientes atendidos por convulsiones afebriles, debería constituir indicación para una valoración cardiológica ulterior y/o seguimiento futuro.
7. El ECG permite diferenciar condiciones cardiológicas y neurológicas, co-existentes o menos en el mismo paciente.
8. El ECG permite estratificar el pronóstico de aquellos pacientes diagnosticados de patologías neurológicas, aunque este aspecto se tiene que estudiar ulteriormente en pacientes pediátricos.
9. Al menos unas canalopatías (como el síndrome de Brugada), deberían de considerarse como patologías evolutivas: a este respecto, la forma que tenemos de valorar el ECG pediátrico tendría probablemente que cambiar. Estudios futuros tendrían que enfocarse en como los trazados de unas poblaciones seleccionadas de niños podrían cambiar en la edad adulta.

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